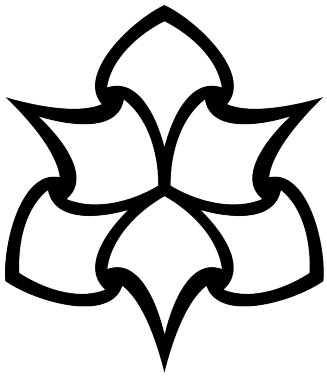

Neuromuscular Impairments to Flexibility and Strength in Adults with Muscular Dystrophy: Acute Response to Physiotherapy

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Contents

Publications

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Morse, C. I., Bostock, E. L., Twiss, H. M., Kapp, L. H., Orme, P., & **Jacques, M. F.** (2018). The cardiorespiratory response and physiological determinants of the assisted 6-minute handbike cycle test in adult males with muscular dystrophy. *Muscle & nerve*. DOI: 10.1002/mus.26146.

Bostock, E. L., Edwards, B. T., **Jacques, M. F.**, Pogson, J. T., Reeves, N. D., Onambele-Pearson, G. L., & Morse, C. I. (2018). Impaired glucose tolerance in adults with duchenne and becker muscular dystrophy. *Nutrients*, *10*(12), 1947.

Jacques, M. F., Stockley, R. C., Bostock, E. I., Smith, J., DeGoede, C. G., & Morse, C. I. (2019). Frequency of reported pain in adult males with muscular dystrophy. *PloS one*, *14*(2), e0212437.

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Table List

Abbreviations

Active Range of Motion (ROM^{Active})

Activities of Daily Living (ADL)

Anatomical cross sectional area (ACSA)

Analysis of Variance (ANOVA)

Average Daily Total Minutes of Physical Activity (TPA^{Mins})

Becker's Muscular Dystrophy (BMD)

Bioelectrical Impedance (BIA)

Body Mass (BM)

Body Mass Index (BMI)

Bone and Physical Activity Questionnaire (BPAQ)

Centimetres (Cm)

Checklist Individual Strength (CIS)

Control (CTRL)

Dorsiflexion (DF)

Dual-Energy X-Ray Absorptiometry (DEXA)

Duchenne Muscular Dystrophy (DMD)

Facioscapulohumeral Muscular Dystrophy (FSHD)

Fat Fraction Percentage (FF%)

Gastrocnemius Medialis (GM)

Gastrocnemius Medialis Length (L^{GM})

Intra-Class Correlations (ICC)

Kilograms (Kg)

Knee Extension Maximal Voluntary Contraction (KEMVC)

Lean Body Mass (LBM)

Limb-Girdle Muscular Dystrophy (LGMD)

Magnetic Resonance Imaging (MRI)

Manual Muscle Testing (MMT)

Maximum Passive Plantar-Flexion (Max $PF^{Passive)}$

Maximum Passive Dorsi-Flexion ($DF^{Passive}$)

Maximum Active Plantar-Flexion (PF^{Active})

Maximum Active Dorsi-Flexion (DF^{Active})

Maximal Voluntary Contraction (MVC)

Medical Research Council Percentage (MRC%)

Metabolic Equivalent Tasks (METs)

Minimal Detectable Change (MDC)

Myotendinous Junction (MTJ)

Muscle-tendon unit (MTU)

Muscle-tendon unit length (L^{MTU})

Muscular Dystrophy (MD)

Muscular Dystrophy United Kingdom (MDUK)

Myotonic Dystrophy (DM)

Newton's (N)

Newton Metres (N·m)

Nottingham Extended Activities of Daily Living (NEADL)

Pain Visual Analogue Scale (Pain VAS)

Passive Range of Motion ($ROM^{Passive}$)

Physical Activity (PA)

Physical Activity Scale for Individuals with Physical Disabilities (PASIPID)

Plantarflexion (PF)

Plantarflexion Maximal Voluntary Contraction (PFMVC)

Quality of Life (QoL)

Quantitative Muscle Testing (QMT)

Range of Motion (ROM)

Sedentary Behaviour (SB)

Percentage of waking hours in sedentary behaviour (SB%)

Short Form 36 Health Survey (SF36)

Short Form 36 Health Survey version 2 (SF-36V2)

Standard Deviation (SD)

Standard Error Measurement (SEM)

Tendon Length (L^{Tendon})

Tibia Length (L^{Tibia})

Tibialis Anterior (TA)

6 minute walk distance (6MWD)

Abstract

Muscular dystrophy (MD) is a set of progressive muscle wasting conditions characterised by progressive muscle weakness and limited range of motion (ROM). Current evidence of these clinical features, their associations and impacts on quality of life (QoL) are however, largely focussed on children with Duchenne MD (DMD). By comparison, quantified evidence of these features remains limited in adults with Becker's MD (BMD), Limb-Girdle MD (LGMD) and Facioscapulohumeral MD (FSHD), and unreported in adults with DMD. Current guidance on living with MD encourages physical activity (PA) and physiotherapy as methods to maintain health and function, however the understanding of PA and the effectiveness of physiotherapy, remains limited in its reporting in adults with MD. Therefore, the aim of this thesis was to quantify lower limb strength and ankle ROM in adults with MD, identify the associations of these clinical features and the impact of muscle weakness on QoL, measure the effectiveness of physiotherapy on ROM, and quantify the progression of muscle weakness, in adults with MD. Healthy adult controls (CTRL) were shown to have greater maximal voluntary contraction (MVC) of plantar-flexion (PFMVC) and knee extension (KEMVC), ROM measures of passive ROM ($ROM^{Passive}$) and active ROM (ROM^{Active}) than adults with DMD (75%, 92%, 66%, 82%), BMD (51%, 41%, 34%. 55%), LGMD (58%, 53%, 45%, 60%) and FSHD (35%, 25%, 35%, 56%). KEMVC and PFMVC were positively associated with 10m walk time in ambulant adults with MD (r= 0.484 and r= 0.502), and PFMVC was associated with ROM^{Active} in all adults with MD (r= 0.376-.750). Strength (KEMVC) was positively associated with only two domains of QoL, in BMD (r= 0.544 and r= 0.609). By comparison, activities of daily living (positively), self-efficacy (positively), pain (negatively) and fatigue (negatively) were more consistently associated with QoL in adults with MD. The stiffness properties of the Gastrocnemius Medialis (r= -0.494) and muscle tendon unit (MTU) (r= -

0.464) were both negatively associated with $ROM^{Passive}$ in BMD and DMD, respectively. Physiotherapy was shown as effective for acutely improving $ROM^{Passive}$ (19%) and decreasing MTU stiffness (-27%), in adults with DMD. PA was shown to explain both the variance in 10m walk time in ambulant adults with MD (R^2 = 0.540), and the change in lower limb strength over 12 months in adults with BMD (PFMVC, R^2 = 0.585; KEMVC, R^2 = 0.532). Change in lower limb muscle strength in adults with DMD was reported as -19% PFMVC and -14% KEMVC per year. Evidence from this thesis suggests in ambulant adults with MD PA is an important measure to promote to help maintain lower limb strength and function. While in non-ambulant adults with MD a shift in focus to measures of pain and fatigue is required, and that there is some benefit from physiotherapy on the $ROM^{Passive}$ of the ankle in DMD, likely due to reductions in the stiffness properties of the MTU.

Chapter 1

An Introduction to Muscular Dystrophy

1.1 Introduction

Muscular dystrophy (MD) is an umbrella term for a set of myopathic conditions characterised by their progressive muscle wasting nature, leading to loss of ambulation, impaired muscle strength and range of motion (ROM) (Huml, 2015). An estimated 70,000 people in the UK are classified as having a form of MD (Emery, 1991). There are 9 main forms of MD, which are classified dependant on their genetic defect, however characterised on the extent and distribution of muscle weakness, age of onset, rate of progression and severity (Emery, 1991; Emery, 2002). This thesis focusses on four of the most common classifications of MD, Duchenne MD (DMD), Becker's MD (BMD), Limb-Girdle MD (LGMD) and Facioscapulohumeral MD (FSHD). These four classifications of MD, represent the MDs that influence the proteins expressed in the sarco-glycan complex (Huml, 2015). In comparison to the sarco-glycan dystrophies investigated in the present thesis, other MDs are asosociated with genetic defects affecting the muscle nuclear envelope (Emery-Dreyfus MD)(Bonne et al., 1999), or nuclear structure (Congential MD) (Barateau et al., 2017), or only effect the eyes, with no influence on appendicular skeletal muscle function (oculopharengeal MD) (Victor et al., 1962). Myotonic dystrophy (DM), which is the most common form of MD (Emery, 1991), is however not dicussed during this thesis. DM has been extensively researched (Johnson et al., 1995; Harper, 2009; Lindeman et al., 1998). Genetically, DM is associated with the expression of protein kinase and not impairments of the sarco-glycan complex (Brook et al., 1992), and DM uniquely presents with myotonia unlike any of the other forms of MD presented in this thesis (Turner and Hilton-Jones, 2010; Moxley III et al., 2007). In addition, other forms of MD than those addressed in this thesis (DMD, BMD, LGMD and FSHD, see table 1.1) are less common, and it would have been impossible to recruite sufficent samples sizes from these rare forms of MD.

1.2 Incidence, Genetic Presentation and Classification of Conditions

DMD, incidence 3:100,000 (Table 1.1 (Deenen et al., 2015)) and BMD, incidence 2:100,000 (Table 1.1 (Deenen et al., 2015)), are both caused by a deletion or mutation in the coding for the Dystrophin protein, a large structural protein associated with sarcolemma stability (Deconinck and Dan, 2007). Mutations resulting in non-functional dystrophin lead to DMD, while partly functional proteins of abnormal size or shape result in BMD (Emery et al., 2015). The degeneration of muscle from dystrophin deficiency remains unclear, however current theories suggest loss of dystrophin results in increased mechanical stress from sarcolemma destabilisation (Ervasti et al., 1990; Petrof, 1998) and increased calcium influx, causing proteases such as calpains to become activated (Deconinck and Dan, 2007; Morandi et al., 1990). DMD is typically diagnosed by the age of 5 through muscle biopsy and genetic testing, following presentation of symptoms such as a lack of co-ordination and abnormal gait; most individuals become non-ambualtory by the age of 10 (C. McDonald, R. Abresch, et al., 1995). BMD is typically identified at a later age than DMD, with some less severe individuals not identified until adulthood (C. M. McDonald et al., 1995). Muscle weakness is throughout the whole body in DMD and BMD, and progressive by nature, with DMD typically the fastest and most progressive MD condition (Huml, 2015). BMD is slower progressing, with the rate of decline dependant on the extent of dystrophin protein present (Bello et al., 2016).

LGMD, incidence 3:100,000 (Table 1.1 (Deenen et al., 2015)), is the most heterogenous form of MD, with various different genetic types. Despite the genetic sub-classifications of LGMD, all are charecterised by weakness of the hip and shoulder girdles (Bushby, 1999). LGMDs are numbered by their inheritance pattern, as either autosomal dominant (LGMD1) or autosomal recessive (LGMD2), then subcategorised further into an alphabetical system, of order of discovery (eg. LGMD1A was mapped before LGMD1B) (Guglieri et al., 2008). It is worth

nothing that as physical manifestations and functional impairments are described as similar for all LGMDs (Emery, 2002), and for the sake of ensuring consistency with previous descriptions of LGMD (C. McDonald, R. Johnson, et al., 1995; Morse, 2016; Morse et al., 2018), for this thesis sub-classifcations of LGMD have been grouped, and hereafter are referred to as LGMD only.

FSHD, incidence 4:100,000 (Table 1.1 (Deenen et al., 2015)), is a classification which is named after the muscles that are first affected, i.e. the facial and shoulder girdle muscles, with muscle weakness progressing to proximal muscles (Padberg, 2009). Similar to LGMD, FSHD can be split into autosomal dominant (FSHD1) and autosomal recessive (FSHD2) (Sacconi et al., 2015). Both FSHD1 and FSHD2 result from incorrect expression of *DUX4* in differentated tissues, however the pathophysiological mechanism remains undefined (Tawil, 2008). As with LGMD, for this thesis FSHD1 and FSHD2 have been grouped, and hereafter are termed FSHD.

Table 1.1 Mean prevalance rate of muscular dystrophy classifications.

Condition	Mean prevalence rate (per 100,000)
Duchenne MD	3
Becker's MD	2
Facioscapulohumeral MD	4
Limb-Girdle MD	3
Emery Dreifuss Dystrophy	0.3
Oculopharyngeal MD	0.1
Myotonic Dystrophy	10
Congenital MD	0.8
Non-dystrophic myotonia	1

Table 1.1. Mean prevalance rate of Muscular Dystrophy classifications. MD = Muscular Dystrophy (Deenen et al., 2015)

1.3 Clinical and functional presentation of the MD conditions, the classical perspective.

The following sections briefly outline some of the key outcome measures commonly used to describe the severity and progression of MD. These outcome measures are described in further detail throughout the thesis where relevant.

1.3.1 Muscle Strength

The degenerative nature of MD is commonly associated with progressive muscle weakness and limited ROM (Bakker et al., 2002; Yılmaz et al., 2004; Gaudreault et al., 2009; Hyde et al., 2000). Emery (2002) presented the classical understanding of muscle weakness in MD, with muscle weakness presented as whole body in DMD and BMD, while FSHD and LGMD by definition presented with muscle weakness affecting the face/scapula/calves and limb girdles, respectively (Figure 1.1: A = DMD and BMD, B = LGMD, C = FSHD). Ambulation is typically lost from the age of 12 in DMD and between the ages of 20-40 in BMD, while the severity, progression and age of onset typically determining ambulatory status in FSHD or LGMD (C. M. McDonald et al., 1995; C. McDonald, R. Abresch, et al., 1995; C. McDonald, R. Johnson, et al., 1995; Kilmer et al., 1995). The progressive muscle weakness and muscle wasting observed in all of these conditions results in an impaired ability to perform functional tasks such as the 10m walk, rise from the floor and stair climbing (Mathur et al., 2010; Alfano et al., 2013). PA is promoted as a measure to maintain muscle mass and function within MD (Muscular Dystrophy Campaign, 2014). Muscle strength is presented cross-sectionally in Chapter 4 and longitudinally in Chapter 8 as a primary outcome measure, and in chapters 5-7 as a secondary outcome measure, due to its significance as a defining clinical feature of MD.

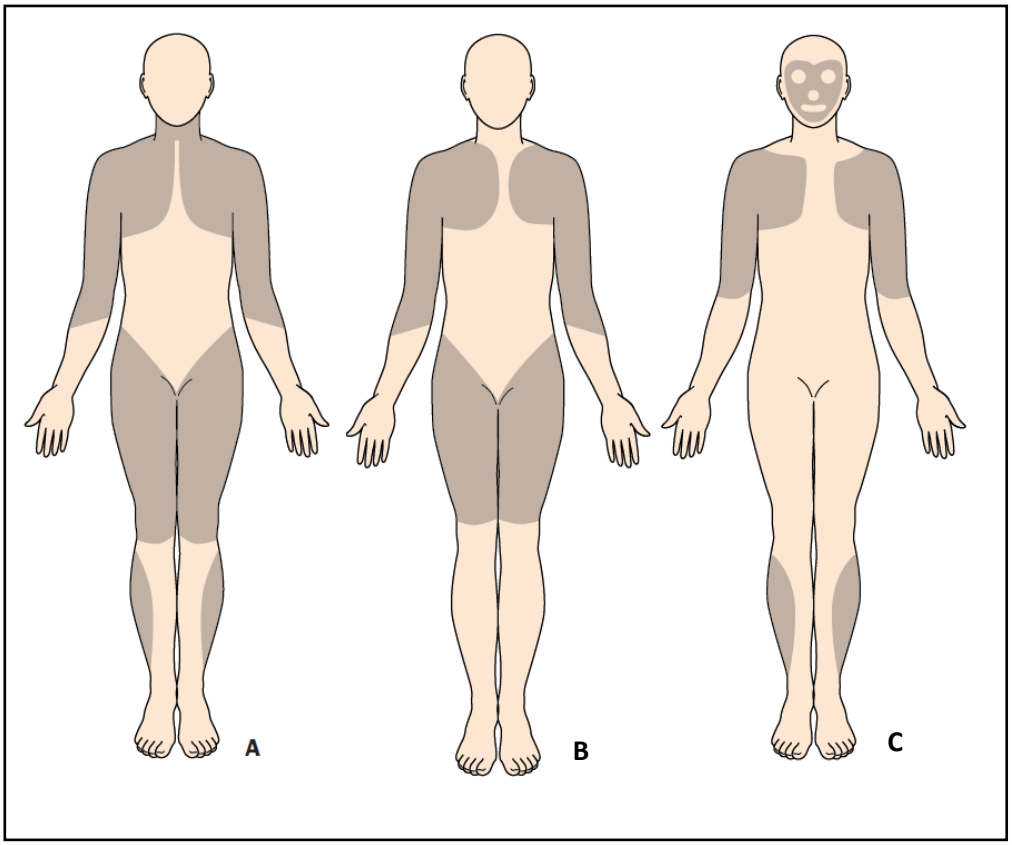

Figure 1.1. Classical Presentation of Muscle Weakness in MD. A = DMD and BMD, B = LGMD, C = FSHD. (Emery, 2002).

1.3.2. Muscle Morphology

As with progressive muscle weakness, the patterns of muscle mass loss are reflected and consistent (and commonly described) as in Figure 1.1. The patterns of muscle mass loss depicted in Figure 1.1 however are reflective of contractile tissue loss, as the size of the muscle mass (volume of material within the muscle membrane) may not match the decline of the contractile area. Within DMD for example, there is evidence of whole-body loss of muscle mass with ageing, consistent with the condition being described as “muscle wasting” (Shimizu-Fujiwara et al., 2012). Within the calf muscles of children with DMD however, is an increased muscle size with no relative increase in muscle strength termed psuedohypertrophy (Mathur et al., 2010; Vohra et al., 2015; Jones et al., 1983). Psuedohypertrophy, and the presentation of increased size of the calf muscles, is one of the most defining clinical features

associated with DMD, and in accordance with abnormal gait, is one of the earliest indicators of DMD (Huml, 2015). Psuedohypertrophy has been attributed to increased muscle damage, necrotic processes of muscle degeneration leads to the muscle trying to repair itself, and an inflammatory response (Deconinck and Dan, 2007) resulting in increased calf size (Beenakker et al., 2002). These necrotic and degenerative processes within the muscle lead to a replacement of contractile tissue with non-contractile tissue (Akima et al., 2012). Increased calf size has also been reported in BMD (Jacques et al., 2017), and described as common in LGMD (Bushby, 1999), however it is not seen as a classic presentation in FSHD. Scapular winging however is a common characteristic within FSHD, resultant from weakness of the Serratus Anterior (Giannini et al., 2006). It should be noted, that despite pseudohypertrophy being reported at the whole muscle level in DMD and BMD, reductions in contracile area with an accumulation of non-contractile material have been reported in children with DMD (Vohra et al., 2015; Jones et al., 1983) and adults with BMD, LGMD and FSHD (Gerevini et al., 2016; Løkken et al., 2016). Given that muscle morphology is a clinical feature identified within children with DMD, but also as a limitation of ROM in healthy adults, within this thesis muscle morphology is investigated in Chapter 4, 6 and 8.

1.3.3 Physical Activity

PA and exercise within the general population are recommended in order to maintain and improve muscle strength, general wellbeing and quality of life (QoL) (Chastin et al., 2011; Bize et al., 2007). Historically, individuals with MD had been advised to avoid PA, for fear of exacerbating muscle damage and increasing progression of the conditions (Siciliano et al., 2015). This was due to primary studies into exercise in animal models, specifically MDX mice, which showed increased muscle damage following exercise (Brussee et al., 1997). More recently, individuals with MD have been advised to partake in low-intensity PA in order to

maintain muscle integrity (Campaign, 2014). Therefore, although recommended, the implications of PA and sedentary behaviour (SB) in adults with MD are currently poorly understood and are investigated in Chapters 4 and 8.

1.3.4 Range of Motion

Limited passive ROM ($ROM^{Passive}$) is often present within MD, especially in children with DMD (Archibald and Vignos Jr, 1959), however it has been argued whether limited ROM is a direct characteristic of DMD, or as a direct result from decreased muscle strength (C. McDonald, R. Abresch, et al., 1995). Loss of ability to actively move through joint ROM (ROM^{Active}), as well as static positioning of joint and fibrotic changes in muscle tissue have all been proposed as causes of ROM loss (Bushby et al., 2010). Similarly, following immobilisation and/or muscle weakness, joints such as the ankle can adapt to "gravity-assisted" positions and therefore stay in plantar-flexion (PF) and display limited dorsi-flexion (DF) capabilities, commonly termed equinus deformity (Williams et al., 1984). Within less severe conditions, FSHD, LGMD, and some forms of BMD, limited ROM has been reported following the loss of ambulation (Kilmer et al., 1995; C. M. McDonald et al., 1995; C. McDonald, R. Johnson, et al., 1995). Limited ROM has previously been shown to increase fall risk in ambulant individuals, and cause pain, impair sleep quality, and therefore QoL, in other clinical conditions. Therefore it is important to understand the presentation and limitations of ROM in adults with MD. Limited ROM, as a clinical feature of MD, is investigated in Chapter 6, along with its associations with muscle morphology, stiffness and weakness.

1.3.5 Quality of Life

QoL represents an individual's perception of their physical, mental and social functioning (Brazier et al., 1992), and is a meaningful measure of how a clinical condition may impact an individual. Given the declining muscle strength, and typical loss of independence, associated

with MD, it is theorised that QoL would likely decrease with condition progression, as is shown in children with DMD (McDonald et al., 2010). It is therefore important to understand the impact of muscle weakness on QoL. Reports of QoL in adults with MD however is limited and therefore investigated in Chapter 5, alongside the implications of muscle weakness on QoL.

1.3.6 Physiotherapy in DMD

Thayer et al. (2017) reported a 10-fold increase in healthcare costs in DMD compared to age matched CTRL, with a particular increase post the age of 16 and into adulthood, primarily due to hospital admissions. No cure for MD is currently available; yet steroid and drug therapy is a primary focus to maintain and improve functional impairments (Daftary et al., 2007; Hawker et al., 2005). Therapeutic techniques however, are a priority for those living every day with this range of conditions. Physiotherapy sessions are currently promoted and actively encouraged by Muscular Dystrophy UK (MDUK) (MDUK, 2016), however data regarding its effectiveness remains unreported. It is therefore important to understand if physiotherapy is an effective non-pharmaceutical intervention in adults with DMD, and to provide further guidance for physiotherapists. Physiotherapy as an effective intervention and mechanistic changes to improve ROM, in DMD is investigated in Chapter 7.

1.3.7 Natural History

Natural history is the term used to describe the progression of a condition or a disease over a period of time, typically 12 months or longer. DMD and BMD are progressive muscle wasting conditions, therefore loss of muscle strength and muscle tissue is likely with clinical progression (Huml, 2015). The natural history of strength changes in children with DMD is well described and reported (C. McDonald, R. Abresch, et al., 1995; Henricson et al., 2013), and DMD is historically recognised as the most progressive MD (Brooke et al., 1989). BMD by comparison is seen as a relatively milder condition, with descriptions of longitudinal changes

limited (C. M. McDonald et al., 1995). Given the progressive nature of MD, it is important to understand the natural progression of these conditions. One year changes in muscle strength, body composition and muscle morphology, of adults with DMD and BMD, is investigated in Chapter 8.

1.4 The Neuromuscular Centre

The Neuromuscular Centre (NMC) is a nationally recognised centre of excellence for adults with neuromuscular conditions. The NMC was established in 1989 by two physiotherapists from a nearby specialist school, who aimed to continue the management and physiotherapy practice that is readily available for children with neuromuscular conditions. For adults with neuromuscular conditions however, provision of services have been commonly reported as lacking (Hill and Phillips, 2006).The NMC does not receive any funding from the NHS, therefore is an established charity, requiring over £1 million annually to run (ref).

Since its establishment in 1989, The NMC has grown to now have more than 700 adults with Neuromuscular Disorders registered. The NMC was originally set up for the provision of physiotherapy for adults with neuromuscular disorders, for which the department has now expanded to employ 5 fulltime physiotherapists specialising in clinical/neuromuscular conditions, and 4 fulltime physiotherapy assistants. Physiotherapy is provided to attendees on a weekly, bi-weekly or monthly basis, following a referral to the centre by a clinician. Regularity of physiotherapy is typically determined by severity of condition (more severe conditions typically attend more frequently), and locality to the centre (more local individuals typically attend more frequently than non-locals). Physiotherapy sessions are typically one hour long, and consist of passive stretching and active-assisted movements (these are outlined in more detail in Chapter 3 and 7), depending on the condition (i.e. more severe conditions will typically focus on passive stretching, while less severe conditions will be a

combination of passive and active-assist movements. Whilst individuals may attend the NMC through referral for physiotherapy and condition management, the unique sense of community and meeting other adults with neuromuscular conditions is key to The NMC, with the psychosocial, as well as physical benefits reported by its users (Hartley and Stockley, 2013; Hartley et al., 2011; Campaign, 2008). These psychosocial benefits are likely enhanced by the dedication by the NMC to its service users, whereby the NMC offers employment to up to 20 adults with neuromuscular conditions, in addition to providing training for web design.

1.5 This Thesis

The aims of this thesis are to provide information on strength, physical activity, passive and active ROM and QoL measures in adults with MD, with comparisons across 4 different classifications of MD (DMD, BMD, LGMD, and FSHD) and a healthy CTRL GROUP. In addition, as well as measurement of typical MD clinical features, this thesis aims to identify associations and mechanisms of identified impairments. In addition, this thesis will assess the acute responses of muscle strength and flexibility to physiotherapy, and the longitudinal changes in body composition, strength and physical activity.

The subsequent literature review will outline the extant research that describes the above identified presentation of muscle strength, ROM, QoL, physiotherapy interventions and natural history in adults with MD. The aim of which is to provide an overview of the current evidence, in support of and contrasting to, the classical understanding of MD presented here.

Chapter 2

Literature Review

2.1 Introduction

MD is a varied yet unique set of conditions, generalised by progressive muscle weakness and development of contractures (Huml, 2015). This literature review will first comment on the limitations of DMD research, then explore and discuss, within the MD classifications identified in Chapter 1, the extant evidence in agreement and contrast with the 'Classical Perspective' presented in Chapter 1, of muscle weakness, muscle morphology, QoL, ROM, natural history and physiotherapy. This literature review is a selective, narrative review (Ressing et al., 2009), presenting MD data with CTRL comparisons only for discussion. This approach was conducted as there are insufficient studies with which to conduct a meta-analysis approach of the outcome measures (These are addressed individually below e.g. 2.2). Throughout the course of the thesis (Oct 2015-July 2018) literature reviews were conducted using Google Scholar, Pubmed, Scopus and ScienceDirect, using search terms using the group (MD, FSHD, DMD, BMD, LGMD) and outcome measure of interest (MVC, ROM, QoL etc.). As limited study data is available from adult populations with MD, there are instances where examples had to be considered from children, again rendering this approach incompatible with that of a meta-analysis. Where relevant this is discussed in the subsequent thesis.

2.2 DMD Research

MD research is heavily centred on DMD, specifically in children, with a recent commentary identifying the need for research in adults with DMD (McDonald and Mercuri, 2018; Pandya et al., 2018). Three primary reasons have been proposed for this, which are as follows (Bettolo et al., 2016; Rahbek et al., 2005; Pandya et al., 2018; Eagle et al., 2002; Bachasson et al., 2014; Lott et al., 2014): 1) Life expectancy has historically been up to the age of approximately 20 years old, and has only improved in the last few decades due to greater respiratory and cardiac care. 2) There is better access to paediatric groups of DMD due to the provision of

support for attendance at specialist treatment centres. Once approaching adulthood, individuals with MD typically lose funding and care through National Health Service (NHS), and so access to large enough samples becomes difficult. 3) Interventions are typically implemented while participants still have a relative maintenance of function.

The subsequent sections of this literature review will assess the relevant literature across DMD, BMD, LGMD and FSHD when possible. Given the severity and focus of research on DMD, the majority of current literature is within paediatric populations with DMD.

2.3 Lower Limb Muscle Size

Despite there being sites of weakness symptomatic for each of the four MDs under consideration, all are characterised by a decline in functioning muscle mass (Kilmer et al., 1995; C. M. McDonald et al., 1995; C. McDonald, R. Abresch, et al., 1995; C. McDonald, R. Johnson, et al., 1995). As described in Chapter 1 and reviewed previously (Emery, 2002), the patterns of muscle loss are presented as whole-body within DMD and BMD, and largely consistent, although not limited to, the body regions within the names of LGMD (hip and shoulder girdles) and FSHD (face, scapula and upper arms). Despite these often reviewed and reported declines in muscle mass, the presented research describing these changes are somewhat lacking. Within DMD for example, despite muscle wasting being characteristic of the condition, in children there is “pseudohypertrophy” of the calf area. This increase in muscle size with no relative increase in strength (Mathur et al., 2010; Vohra et al., 2015; Wokke et al., 2014) is associated with an inflammatory response from the breakdown of muscle and replacement with non-contractile tissue (Jones et al., 1983). Consistent with the description of the progressive nature of DMD, within adults there is only lower limb comparative data from the Gastrocnemius Medialis (GM) (Morse et al., 2015) and Tibialis

Anterior (TA) (Morse, 2016), which both report much smaller muscle size than CTRL comparisons.

Unlike children with DMD, lower limb muscle size in BMD is greatly under reported. Despite a historical description of psuedohypertrophy of the calves (C. M. McDonald et al., 1995; Bradley et al., 1978), only two papers having previously reported lower limb muscle size in adults with BMD (Jacques et al., 2017; Løkken et al., 2016). Løkken et al. (2016) reported no difference in muscle size of the triceps surae compared to healthy CTRL. In contract, Jacques et al. (2017) reported increased GM anatomical cross sectional area (ACSA) in adults with BMD compared to healthy age matched CTRL, however upon further analysis; increased GM ACSA was only evident in non-ambulatory adults. This is likely reflective of the milder and slower nature of this condition, but also suggests that exercise and PA in ambulant adults with BMD may help maintain contractile muscle mass, delaying the onset of psuedohypertrophy. In FSHD psuedohypertrophy is not described as a typical characteristic (Kilmer et al., 1995). In comparison, psuedohypertrophy of the calf has been described as common in LGMD (Bushby, 1999), the only reported measurement of triceps surae in LGMD however, did not report an increase in muscle size compared to CTRL (Løkken et al., 2016).

Current reports of quantified muscle size of the four dystrophic conditions of this thesis with CTRL comparisons are presented in Figure 2.1. For clarity, muscles have been presented as either plantar-flexor (PF) or dorsi-flexor (DF) muscle groups, dependant on the movement they are associated with. This highlights the termed psuedohypertrophy within children with DMD, and the limited reports of muscle size in adults with DMD.

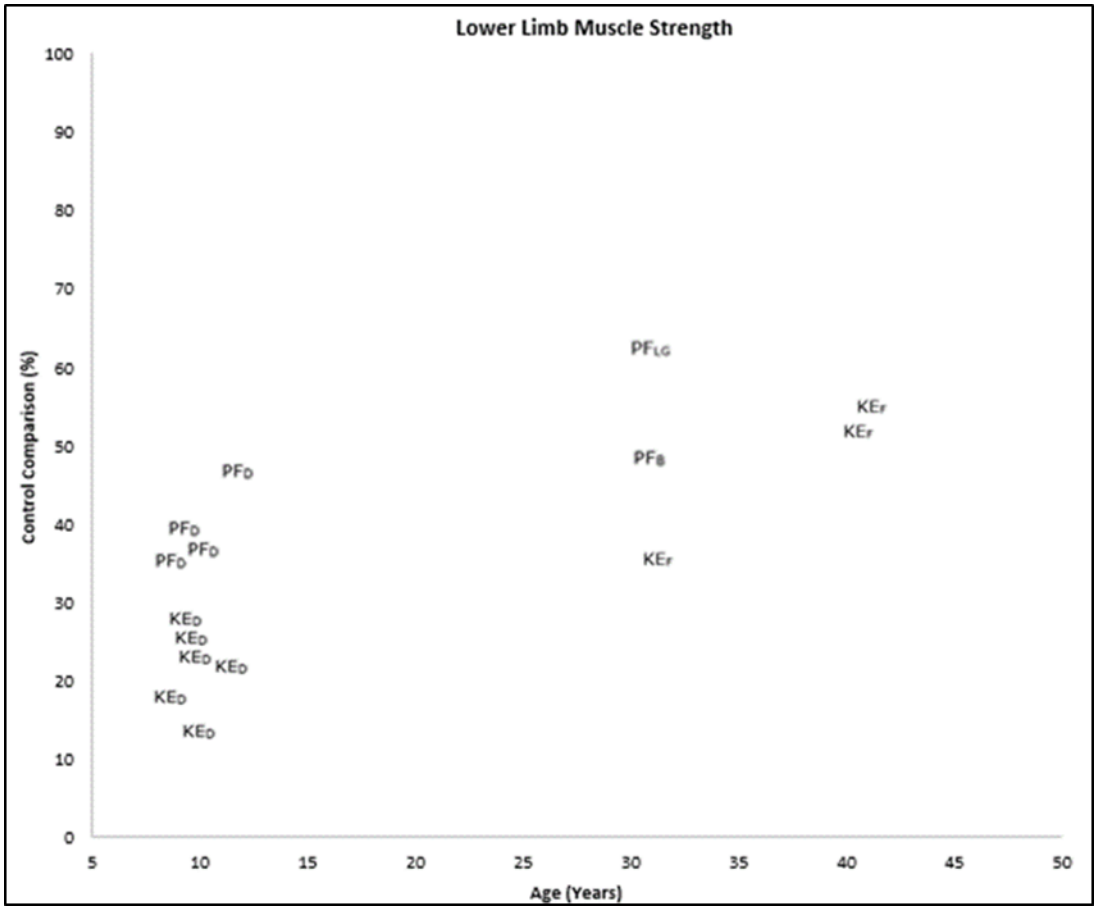

Figure 2.1. Muscle size of DF and PF muscles in DMD, BMD, LGMD and FSHD, presented as percentage comparisons relative to CTRL participants. Data is presented as the mean age of participants groups (X axis) to show the lifespan comparisons, and muscle size as percentage of CTRL (Y axis). PF = Muscles associated with plantar-flexion, DF = Muscles associated with dorsi-flexion. $_{D}$ = Duchenne muscular dystrophy; $_{B}$ = Becker's muscular dystrophy; $_{LG}$ = Limb-Girdle muscular dystrophy; $_{F}$ = Facioscapulohumeral muscular dystrophy' (Mathur et al., 2010; Vohra et al., 2015; Forbes et al., 2013; Wokke et al., 2014; Jones et al., 1983; Huml, 2015; Morse, 2016; Morse et al., 2015; Jacques et al., 2017; Løkken et al., 2016)

2.4 Strength in MD

2.4.1 Measurement of Strength in MD

Measurement of muscle strength in MD, given its progressive nature, has been a focus of research for a long time (C. M. McDonald et al., 1995; C. McDonald, R. Abresch, et al., 1995;

Kilmer et al., 1993). Within MD, these descriptions of strength are often reported using physiotherapist assessment scales, such as the Manual Muscle Test (MMT) and the adapted MMT by Medical Research Council (MRC%) (Florence, 1984). MMT and MRC% are based on an individual's resistance to movements from an assessor, typically a physiotherapist, and rated weak to strong on a 5-point scale (MMT), or converted to a 10 point scale and expressed as a percentage of the maximum score possible (MRC%) (Mendell and Florence, 1990; Florence et al., 1992). MMT and MRC% have the benefit of not requiring any equipment, however, both rely on subjective judgement and have therefore been questioned for reliability, validity and sensitivity to change (Cuthbert and Goodheart, 2007; Bohannon, 2005; Mayhew et al., 2007) and are better classified as muscle strength assessments, rather than muscle strength measures.

Myometry, the use of a handheld dynamometer to quantify the force of a movement, is an alternative measure of muscle strength (Schwartz et al., 1992). Myometry requires a practitioner to provide the resistive force to a movement while holding the handheld dynamometer, which measures the force produced by the participant, and can be used to measure force from up to 13 muscle groups (Van der Ploeg et al., 1991). Myometry is a more sensitive measure of muscle strength than MMT and MRC%, and due to its accessibility is commonly used in clinical randomised CTRL trials and longitudinal studies (C. M. McDonald et al., 1995; McDonald et al., 2013). Issues have been noted however, for the reliability (ICC = 0.72-.91) and validity of myometry. Limitations include a maximum attainable force in many handheld dynamometers, limiting its possible use to some of the more less-abled conditions (Stuberg and Metcalf, 1988). In addition, Sloan (2002) and Bohannon (1999), in children and adults respectively, reported issues of stabilisation, as well as myometry being dependent upon resistance from an assessor.

Quantative Muscle Testing (QMT) is a measurement system typically using a force transducer or strain gauge with straps to a mechanical 'anchor'. The use of a mechanical 'anchor' in QMT, which the force transducer is attached to, to provide resistance, provides a more objective measure than resistance from an assessor as seen in myometry. QMT has been shown to be a reliable measure of muscle force across 9 strength measures, with high ICC for CTRL (0.91-.96) and FSHD participants (0.86-.96), as well as Intrarater Class Coefficients (0.91-.99) in the FSHD participants (Personius et al., 1994). Furthermore, QMT was shown to be more reliable than MMT, as the same study reported MMT Interrater Class Coefficients = 0.5-1 and Intrarater Class Coefficients = 0.79-.98 (Personius et al., 1994). Similarly, Brussock et al. (1992) utilised a similar method of QMT, using an electronic strain gauge, which reported a high ICC (0.88-.99) across 8 muscles in children with DMD. QMT has become a common method of strength measurement for use in populations that exhibit a wide range of muscle strength, such as FSHD (Janssen et al., 2014; Wokke et al., 2014; Wilson et al., 2018). Primarily the use of mechanical resistance allows for more accurate and reliable measurements in stronger and more functional individuals than myometry (Personius et al., 1994), as well as in lower strength and less functional individuals (Brussock et al., 1992).

Measurement of lower limb strength using wholly mechanical QMT systems, rather than the strain gauges and straps associated with typical QMT (Personius et al., 1994), is limited within the literature to more able bodied and ambulant MDs, such as children with DMD or younger and milder forms of other MDs (Mathur et al., 2010; Løkken et al., 2016; Lerario et al., 2012). These strength measurements are also typically limited to one or two movements (usually associated with the knee or ankle). This is primarily due to difficulties in mobility and mechanics of positioning to allow such testing in the more severely affected individuals. More specifically, this would require the use of a hoist, and difficulties in body positioning and self-

support, given the nature of whole body contractures in some participants (Johnson et al., 1992). Testing of only ambulant, or more able-bodied individuals, is unrepresentative of these populations, where many result in eventual reliance upon wheelchairs and/or walking aids (Bushby et al., 2010; Pegoraro and Hoffman, 2012; Pandya et al., 2008). This highlights the requirement for greater adaptability in the procedures and techniques used to assess muscle strength, such as QMT, or adaptations thereof.

2.4.2 Lower Limb Muscle Strength Comparisons

Progressive muscle weakness is a defining clinical feature of MD, with impaired MVC of knee extension (KEMVC) and plantar flexion (PFMVC) influencing QoL in children with DMD, and the ability to perform functional measures in children with DMD and adults with BMD (Alfano et al., 2013; Bendixen et al., 2014; Mathur et al., 2010). Emery (2002) presented areas of predominant areas of weakness in MD (Figure 1.1), presenting DMD and BMD as whole body progressive muscle weakness conditions, LGMD with weakness associated with the hip and shoulder girdles, and FSHD with weakness focussed on shoulder girdles and dorsi-flexors. Below describes evidence of muscle weakness in MD in comparison with healthy CTRL, and is summarised in Figure 2.2.

As noted previously, extensive research has examined muscle strength in children with DMD, where KEMVC was 72-87% lower than CTRLs across six studies (Akima et al., 2012; Lott et al., 2014; Mathur et al., 2010; Skalsky et al., 2009; Wokke et al., 2014; Lerario et al., 2012). Furthermore, PFMVC was 54-65% lower than CTRLs across four studies in children comparisons (Lott et al., 2014; Mathur et al., 2010; Wokke et al., 2014; Vohra et al., 2015). To date, no lower limb muscle strength has been reported for adults with DMD.

Across the three other MD classifications identified for this thesis, one paper reported PFMVC as 52% and 38% lower than CTRL in BMD and LGMD, respectively (Løkken et al., 2016). PFMVC in adults with FSHD however has not been compared to CTRL. Comparatively, KEMVC was reported as 45-65% lower than CTRL in adults with FSHD within three studies (Bachasson et al., 2014; Skalsky et al., 2008; Wilson et al., 2018). KEMVC has not been reported against CTRL in either adults with BMD or LGMD, despite previous recognition of the relationship between KEMVC and functional tasks in adults with BMD (Alfano et al., 2013).

In summary, lower limb muscle strength with CTRL comparisons is only reported in children with DMD, while in adult populations of BMD, LGMD and FSHD, there are no CTRL comparisons of specifically KEMVC in adults with BMD and LGMD, and PFMVC in adults with FSHD. Current MD lower limb strength comparisons to CTRL are summarised in Figure 2.2.

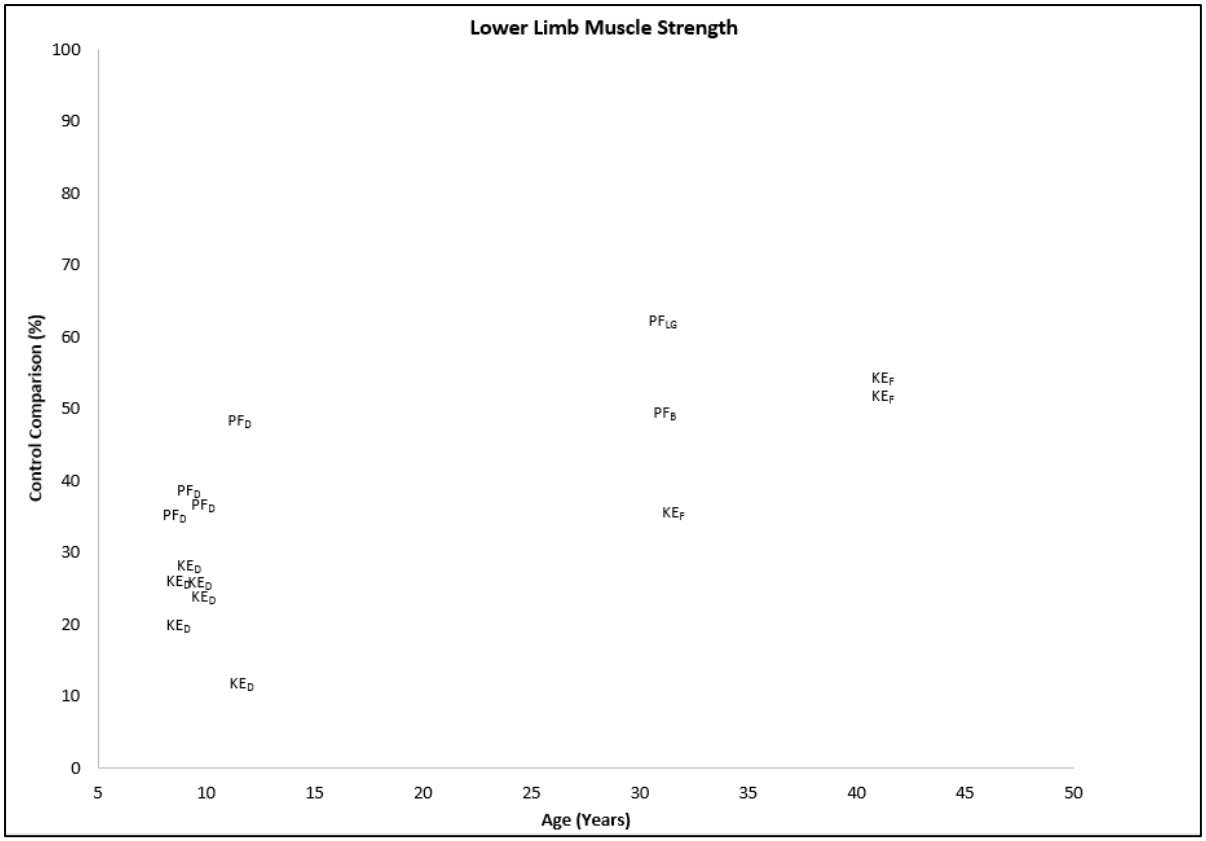

Figure 2.2. Percentage muscle strength of PFMVC and KEMVC in DMD, BMD, LGMD and FSHD, based on comparisons relative to CTRL participants. Data is presented as the mean age of participants groups (X axis) to show the lifespan comparisons, and muscle strength as percentage of CTRL (Y axis). PF = Plantar-flexion maximal voluntary contraction; KE = Knee-extension maximal voluntary contraction $_{D}$ = Duchenne muscular dystrophy; $_{B}$ = Becker's muscular dystrophy; $_{LG}$ = Limb-Girdle muscular dystrophy; $_{F}$ = Facioscapulohumeral muscular dystrophy' CTRL = Control. (Bachasson et al., 2014; Forbes et al., 2013; Lott et al., 2014; Akima et al., 2012; Mathur et al., 2010; Skalsky et al., 2008; Skalsky et al., 2009; Wilson et al., 2018; Lerario et al., 2012; Løkken et al., 2016; Vohra et al., 2015; Wokke et al., 2014)

2.5. Physical Activity and Sedentary Behaviour

PA is commonly defined as the expenditure of energy greater than 1.5 Metabolic Equivalent Tasks (METs), while SB is defined as 1.5 METs or less (Tremblay et al., 2010; D. J. Ryan et al.,

2018). Healthy adults are suggested to participate in 30 minutes of moderate PA (3-6 METs) five days a week or 20 minutes of vigorous PA (6+ METs), 3 days a week, in order to maintain and promote health (Haskell et al., 2007). Higher PA and lower SB are linked to better musculo-skeletal and cardio-metabolic health in the general population (Peterson et al., 2013; Gianoudis et al., 2015; Tremblay et al., 2010; Henson et al., 2013). The clinical progression and progressive muscle weakness may predispose those with MD to higher levels of SB and limit PA, with recent evidence of increased obesity reported in non-ambulant adults with BMD compared to ambulant adults (Jacques et al., 2017). PA is promoted by Muscular Dystrophy UK (MDUK) (Campaign, 2014) as a method to maintain health and function when possible, however there is currently limited research in PA levels in neuromuscular conditions, and more specifically, MD (Jimenez-Moreno et al., 2017).

PA assessments have been presented in children with DMD using subjective methods such as questionnaires (Baecke Physical activity questionnaire (Hawker et al., 2005); Short-Form 36 Health Assessment (SF36: however the SF36 does not contain a PA domain, more likely this study has used the Physical Function domain of the SF36 to represent PA)(Abresch et al., 2002); Self developed Physical activity questionnaire (Heutinck et al., 2015)), all reporting reduced PA in DMD groups. McDonald et al. (2005) and Davidson et al. (2015) both used objective measures of step count activity in children and adolescents with DMD, both reporting significantly reduced step count in DMD. Davidson et al. (2015) remains currently the only paper linking PA (step count) with functional measures, with a strong correlation between PA and the 6 minute walk distance (6MWD) ($r= 0.80$). Objective measures of PA using accelerometry (Jeannet et al., 2011; Ferguson et al., 2016) (DMD and FSHD) and doubly labelled water (Elliott et al., 2015) (DMD) have both been used in MD, however the DMD studies were in children, and no CTRL group was used in either study. While objective

measures of PA has only been reported in ambulant children with DMD, PA remains possible even following the loss of ambulation, such as through the use of adapted exercise equipment, which has previously been shown to maintain muscle function in DMD (Jansen et al., 2013). All current reports to date have focussed on PA, SB however can be an independent predictor of impaired health and wellbeing (Park, 2017; D. Ryan et al., 2018), and remain prevalent even when PA guidelines are met (Craig et al., 2009; Ryan et al., 2015). No study has yet examined SB in adults with MD, nor evaluated its impact on measures of function and wellbeing.

Only two papers have reported PA in adults with MD with a healthy CTRL comparison, both using the Bone and Physical Activity Questionnaire (BPAQ), Jacques et al. (2017) reported lower current PA levels in adults with BMD compared to healthy age matched CTRL. While Morse et al. (2016) reported significantly reduced PA history (using BPAQ) in all MD conditions compared to CTRL, as well as DMD being lower compared to BMD, LGMD and FSHD groups. The use of questionnaire and self-report methods to determine PA however have previously been shown to over-estimate PA and lack objectivity (D. J. Ryan et al., 2018).

Despite the relationships long recognised between lower limb muscle strength and functional outcomes in MD (Alfano et al., 2013; Mathur et al., 2010; McDonald et al., 2013), the relationships between PA and muscle strength in MD remains relatively unexplored, with Morse et al. (2016) reporting a correlation between the Physical Activity Scale for Individuals with Physical Disabilities (PASIPID) and grip strength. Given the lack of PA comparisons in MD, ageing populations can be a useful comparison, particularly as sarcopenia, the loss of muscle size and strength from ageing, becomes prevalent (Morse et al., 2005; Thom et al., 2005). Foong et al. (2015) reported positive associations of PA intensity with lean body mass (LBM)

and lower limb strength in an ageing population, exhibiting a dose-response like relationship, as those that participate in more PA are likely to maintain more muscle strength and contractile tissue. Similarly, Morie et al. (2010) reported positive associations of muscle strength and PA levels in healthy elderly, while Goodpaster et al. (2006) showed that increased PA in elderly populations increased muscle strength and delayed fatty infiltration into the muscles. The association between PA and maintained muscle strength and contractile tissue in ageing populations has also been shown in adults with FSHD, where PA as an intervention reduced fatty infiltrations into muscles, as well as reducing fatigue (Ferguson et al., 2016; Voet et al., 2014). No PA or SB data, measured through accelerometry and with a CTRL comparison, is currently available in adults with MD. Presentation of such findings could provide greater understanding of functional and health impairments, and inform future intervention strategies. Furthermore, understanding of PA and SB will help to further substantiate current guidance in adults with MD.

2.6 Quality of Life (QoL)

QoL is a measure of an individual's perceptions of their own well-being, and is becoming increasingly prominent in clinical assessment and monitoring processes, as a universal method of assessment beyond, but also including, the physical implications of the condition (Graham et al., 2011).

Some of the earliest work into QoL in MD assessed the QoL construct using extremely broad methods of participant recruitment, often assessing QoL in MD as a single combination of classifications (Nätterlund and Ahlström, 2001; Ahlström and Sjöden, 1996), rather than specific classifications. Typically QoL was lower in those with MD, and was associated with disability, impairment and pain (Ahlström and Gunnarsson, 1996; Abresch et al., 2002). The

variations in mutative-genetic cause (Emery, 2002), function (Lue et al., 2009) and clinical progression (Kilmer et al., 1995; C. M. McDonald et al., 1995; C. McDonald, R. Abresch, et al., 1995; C. McDonald, R. Johnson, et al., 1995) of each condition however, strongly suggests that each classification should be recognised and assessed independently.

Within DMD, QoL has been extensively measured in children, typically showing lower QoL, which has been associated with measures of physical function such as the 10m walk time (Messina et al., 2016), KEMVC (McDonald et al., 2010), functional scales (Bray et al., 2010) and 6MWD (Henricson et al., 2013). Associations between clinical outcome measures and QoL however have been shown to reduce with age (Henricson et al., 2013; Messina et al., 2016). Beyond changes in function, the Emotional domain of QoL has been reported as comparable in children with DMD to CTRLs (Bendixen et al., 2012), while Uzark et al. (2012) reported higher Psychosocial domain in older boys with DMD than younger boys, possibly indicating improved coping mechanisms with clinical progression. In adults with DMD however, QoL has only been reported in three studies, the first identifying lower QoL in adults with DMD compared to CTRL except for domains of Mental Health and Role Emotional, which acts as further evidence of improved coping mechanisms with clinical progression (Pangalila, Van Den Bos, Bartels, Bergen, Kampelmacher, et al., 2015). While the second study identified factors of fatigue, pain, anxiety and depression to significantly influence QoL in adults with DMD (Pangalila, Van Den Bos, Bartels, Bergen, Stam, et al., 2015). The third study looked at the associations between QoL in children and adults with DMD (aged 8-33 years old), Kohler et al. (2005) however showed no association between QoL and respiratory function, a clinical measure known to decline with age in DMD and recognised as influenced by clinical progression (Phillips et al., 2001; Brooke et al., 1989). Therefore, further investigation is required to understand QoL in adults with DMD, but also to see if functional impairment

impacts QoL in adults with DMD as seen in children, or if there is a shift to perceptive measures, such as fatigue and pain.

Within FSHD QoL has similarly been assessed across three studies, in which QoL has been shown to be lower than CTRL in domains associated with Physical Function, and shown to be associated with walking function (Aprile et al., 2012). In addition, pain has previously been described as symptomatic of FSHD (Bushby et al., 1998), and has been associated with QoL in adults with FSHD (Morís et al., 2017; Padua et al., 2009). Only one study has compared different MD classifications, and is the only study to include adults with BMD and LGMD (Grootenhuis et al., 2007). BMD were shown to have better QoL on some domains compared to other adults with MD (Grootenhuis et al., 2007), which was suggested to be due to the relatively milder nature of the BMD participants within the study. This study however was largely descriptive of differences in QoL between MD classifications and age (Young vs Old), and therefore offered no mechanistic measure of function, or any other possible co-variates, to associate with higher or lower QoL scores.

To date, comparisons of QoL between different classifications of MD remain limited, with most research containing multiple classifications grouping them together into a single MD. In addition, the impact on QoL of progressive muscle weakness, seen as a defining clinical feature of MD, similarly needs assessing, in comparison to other previously identified QoL associates such as pain and fatigue.

2.7 Range of Motion (ROM)

There are a number of measurements encompassed within the term “flexibility”; in general, it refers to the passive ROM ($ROM^{Passive)}$ around a joint. For example, the $ROM^{Passive}$ from maximum PF to maximum DF is a measure of flexibility within the muscle-tendon unit (MTU)

of the triceps surae. Alternatively, it is possible to describe the stiffness of the elements of the MTU. For example, the passive torque generated during the passive angle change of the joint provides MTU stiffness ($N.m.deg^{-1}$) (Morse et al., 2008). Whereas, tracking the elongation of the myotendinous junction (MTJ) allows for the calculation of the GM stiffness ($N.m.cm^{-1}$) (Morse, 2011). Clinically, limitations in ROM are often referred to as "contractures", this however does not distinguish the mode or region within the MTU that is being assessed, and often lacks quantitative assessment.

The flexibility of the joint, especially the ankle, when stretched to end ROM has been historically recognised as limited in MD (Archibald and Vignos Jr, 1959). Hereafter ROM will refer to ankle ROM, in the sagittal plane from maximum plantar flexion (PF) to maximum dorsiflexion (DF). Limited ROM is reported as a characteristic in children with DMD (Bushby et al., 2010), and reported in adults with BMD, LGMD and FSHD following the loss of ambulation (Kilmer et al., 1995; C. M. McDonald et al., 1995; C. McDonald, R. Johnson, et al., 1995). Within MD, the loss of maximum passive PF (Max $PF^{Passive}$) to maximum passive dorsiflexion (Max $DF^{Passive}$) ROM ($ROM^{Passive}$) at the ankle has been reported in children with DMD (13.6 years) and adults with BMD (20.7 years), LGMD (44.8 years) and FSHD (48.6 years) as 44°, 15°, 47° and 28°, respectively, where values represent a decrease from CTRL, whom typically report a $ROM^{Passive}$ of 60° (Johnson et al., 1992). These reports however lack population homogeneity, with a wide age range of ages within LGMD (9-82) and DMD (1-30 years). In children with DMD, ankle $ROM^{Passive}$ has been associated with lower limb functional status (Archibald and Vignos Jr, 1959). Limited $ROM^{Passive}$ has been reported as rare in ambulant children with DMD but becomes more prevalent in wheelchair users (Ringel et al., 1977), and is often described as associated with levels of muscle weakness in LGMD and FSHD (Kilmer et al., 1995; C. McDonald, R. Johnson, et al., 1995). While $ROM^{Passive}$ has been reported

in MD (Johnson et al., 1992), ROM^{Active}, the ROM that an individual is able to independently move their ankle to, remains unreported. ROM^{Active} is likely to be a more important measure given its likely influence of function and fall risk (Menz et al., 2006; Menz et al., 2005), however remains unreported in adults with MD.

Mechanistic causes of limited ROM have been proposed as fibrotic changes to the muscle, reduced muscle strength to actively move through ROM, and static positioning of the ankle in PF. Investigation into these factors however remains largely unreported (Dubowitz, 1964; Brooke et al., 1989; Hsu and Furumasu, 1993). In animal models, a significant relationship has been identified between collagen content (non-contractile tissue) of the gastrocnemius and level of contracture in dystrophin deficient animal models, specifically *MDX* mice (Garlich et al., 2010). Conversely, increased collagen content of Soleus in *MDX* mice has been reported as having no relationship with muscle stiffness (the passive torque produced with the soleus under stretch) (Smith and Barton, 2014). Muscle stiffness has been shown to be higher in children with DMD than CTRL, measured by ultrasound (Supersonic Shear Imaging) (Lacourpaille et al., 2015). Muscle stiffness however has not been quantified in lower limb muscles of adults with MD, nor has its association with ROM been explicitly reported in human models.

Limited ROM has previously been shown to cause pain (Dalyan et al., 1998; Willig et al., 1995), increase fall risk (Menz et al., 2006), impair sleep quality (Oztura and Guilleminault, 2005), and therefore reduce QoL (Katalinic et al., 2010). The current presentation of limited ROM in MD is restricted to paediatrics with DMD, and in adults with BMD, LGMD and FSHD, however the broad age ranges used previously limits its comparability. Furthermore, while speculated, determinants of ROM remain unquantified in adults with MD.

2.8 Acute Response to Physiotherapy

Physiotherapy, which in MD is typically limited to passive stretching and mobility exercises, is currently encouraged by MDUK as a method of maintaining health and function (MDUK, 2016). Other clinical conditions, such as cerebral palsy, which display muscle weakness (Hussain et al., 2014) and increased stiffness (Hussain, 2013), have reported positive responses to physiotherapy and passive stretching, with outcomes such as decreased muscle stiffness (Pin et al., 2006; Zhao et al., 2011). Within MD however, quantified effects of passive stretching and physiotherapy on ROM is limited, therefore clinical practice is typically guided by expert clinical opinion (Radford et al., 2006).

Hyde et al. (2000) reported ankle ROM reduced with age, synonymous with the progressive nature of the condition, even whilst receiving passive stretching in children with DMD. No specific measure of ROM was reported however, nor was there a non-treatment group against which to compare passive stretching. Hyde et al. (2000) did however report that the progression of ROM loss was reduced in participants receiving a combination of passive stretching and night splints, in comparison to just passive stretching. Similarly, individuals receiving passive stretching as part of multi-component care have been reported to maintain ROM and ambulation for up to 2 years longer than those not receiving care (Vignos and Archibald, 1960; Vignos et al., 1963).

Longitudinal studies have shown some, albeit limited, benefit of stretching in MD. Given the progressive and degenerative nature of DMD, it is important to assess the effectiveness of physiotherapy in adults with DMD, who have developed further limited ROM and weakness, likely from muscle degeneration and increased non-contractile tissue, compared to children with DMD (Willcocks et al., 2014). Furthermore, it is unclear whether changes in ROM with stretching can be attributed to the MTU or the muscle i.e. whether the non-contractile

component limits stretch hence no adaptation to the muscle. At present however, there are no descriptions of the acute outcomes of passive stretching in adults with MD. Therefore further guidance is required as to the effectiveness of physiotherapy as a non-pharmaceutical treatment in adults with DMD.

2.9 Natural History Studies

The progressive nature of DMD means it has been a focus of a wide range of studies to quantify the condition progression, but also as a reference for the effectiveness of steroid treatment (Akima et al., 2012; Bendixen et al., 2014; Elliott et al., 2012; Jansen et al., 2013; Kohler et al., 2005; C. McDonald, R. Abresch, et al., 1995). Natural history studies (the description of disease progression over time) have shown a maintenance of strength in children younger than 7 years old, and a decline in strength in children over the age of 7 (Lerario et al., 2012). Consistent with this, a 15% decline in KEMVC has been shown over a 48 week period, in ambulant children with DMD (Mean age= 8.3) (McDonald et al., 2013). Clinical trials and longitudinal studies have typically used 'clinical endpoints' as a measure of function, typically a 6-minute walk test (Mayhew et al., 2007; McDonald et al., 2010; McDonald et al., 2013). Children with DMD typically lose ambulation by the age of 12 however, therefore clinical endpoint measures of function become redundant (Morse et al., 2018). Two studies have reported annual changes in adolescents/adults with DMD, reporting 1.2-2% decline in KEMVC (13-24 years) (C. McDonald, R. Abresch, et al., 1995; Steffensen et al., 2002), however these studies used MMT and MRC% methods of assessment, previously described as not sensitive to report changes in muscle strength (Chapter 2.4.1). Given the improvements in health care, particularly cardiac and respiratory, life-expectancy is increasing in DMD, with many now living well into adulthood (Bettolo et al., 2016; Rahbek et al., 2005). Comparatively, only one study has assessed change in muscle strength longitudinally in adults with BMD,

however MRC% was used as measure of muscle strength (C. M. McDonald et al., 1995). Therefore further understanding of the progression of these conditions is required.

2.10 Thesis Aims

Based upon the presented literature, sub-classifications of MD have many clinical features, such as progressive muscle weakness, increased muscle size of the calves and limited ROM. Current evidence of these clinical features, their associations and impacts are however largely focussed on children with DMD. By comparison, quantified evidence of these features, their associations and impacts, remains limited in adults with BMD, LGMD and FSHD, and unreported in adults with DMD. Furthermore, current guidance on living with MD encourages PA and physiotherapy as methods to maintain health and function, however the understanding of PA, and the effectiveness of physiotherapy, remains limited in its reporting in adults with MD. Therefore, the aims of thesis are:

Chapter 4: To investigate the relationship between muscle strength and size; establish the relationship between muscle size and strength with objective measures of physical activity, with implications for the maintenance of muscle function in MD.

Chapter 5: Compare the self-reported QoL of adults with DMD, BMD, LGMD and FSHD, and a non-MD CTRL group; Present and compare between groups measures of Muscle Strength, Activities of Daily Living, Fatigue, Pain, Self-Efficacy and BMI; Identify associations between QoL domains and Muscle Strength, Activities of Daily Living, Fatigue, Pain, Self-Efficacy and BMI.

Chapter 6: Compere ROM^{Active} and $ROM^{Passive}$ in adults with MD and CTRL; Compare levels of MTU and GM stiffness in adults with MD and CTRL; Identify associations of ROM with measures of muscle weakness, stiffness and muscle length.

Chapter 7: Quantify the acute effect of physiotherapy on 1) Range of Motion Measures, 2) Stiffness Properties Associated with the ankle as identified in Chapter 7 and 3) Muscle Strength, in adults with DMD.

Chapter 8: Quantify changes, from a one year follow up, in body composition, muscle morphology, muscle strength and physical activity levels in adults with DMF and BMD; Identify the impact of changes in physical activity on body composition and muscle strength in adults with BMD and DMD.

Chapter 3

Methods

3.1 Participants

All MD participants were recruited from The NMC (Winsford), which was described in Chapter 1. This thesis has utilised The NMC to overcome the limitations of participant recruitment, discussed in Chapter 2, whereby the lack of healthcare provision has previously limited accessibility to large populations of adults with neuromuscular disorders. Similarly, this thesis has formed part of a broader partnership between The NMC and Manchester Metropolitan University, whereby research questions from individuals with, or practitioners working with, neuromuscular disorders can be answered. Previous work has identified an end of psuedohypertrophy in adults with DMD (Morse et al., 2015), impaired bone health in adults with MD (Morse, 2016) and calculations for resting energy expenditure as a basis for nutritional guidelines in adults with BMD (Jacques et al., 2017).

In line with this thesis the principal investigator was based at The NMC 5 days a week, where all MD participant recruitment and data collection took place. Therefore, all protocols and data collection techniques were designed to be made around participant's regular physiotherapy appointments, and with the least inconvenience to the participants, but also to not impact on their regular physiotherapy.

3.1.1 Sample Size

Prior to participant recruitment a priori power analysis was used (G Power 3.1, Germany), based on previous means and SD for PFMVC (Løkken et al., 2016), between CTRL and BMD (effect size = 1.28), and CTRL and LGMD (effect size = 2.15), the estimated sample size would

be BMD n = 6, and LGMD n = 14. In addition, based on previous means and SD for KEMVC (Bachasson et al., 2014), between CTRL and FSHD (effect size = 1.60), the estimated sample size for FSHD would be n = 10. Therefore sample sizes of MD and CTRLS are comparable, or indeed higher than those suggested by the power analysis. Furthermore, the comparable participant sample sizes of independent MD and CTRL groups are largely consistent with previous research into these conditions, for example previous participant numbers have been CTRL n = 14, FSHD n = 17(Skalsky et al., 2008); CTRL n = 13, n = 21(Mathur et al., 2010); in CTRL n = 19, FSHD n = 19(Bachasson et al., 2014).

3.1.2 Recruitment

MD participants were recruited from the NMC, for which all were male, as DMD and BMD are x-linked conditions, to therefore allow cross- condition comparisons. Participants were typically recruited during their standard physiotherapy session. Due to the variety of neuromuscular disorders that utilise the services of The NMC, the physiotherapists with access to diagnosis were often the first point of recruitment. Whereby physiotherapists were briefed by the principal investigator of the criteria of participants (Male, aged 18-55, conditions of DMD, BMD, LGMD or FSHD, attend the NMC a minimum of once a month). Participants were often offered the chance to take part in research during their standard physiotherapy session, following a briefing session from the principal investigator. If an individual expressed an interest in taking part in the research, the principal investigator was at the centre to discuss the research, give the participant an information sheet (Appendix 1) and answer any questions. In addition to recruitment through physiotherapists, the principal investigator also actively recruited through interaction with individuals during their visits to the NMC. The healthy CTRL group were recruited using poster advertisements (Appendix 2) at Manchester Metropolitan University.

A total of 77 adult males volunteered for the studies within this thesis, of which 61 were adults had been previously diagnosed with a type of MD on referral to the NMC. Table 3.1, below, presents the numbers of individuals in each of the MD classifications relevant to this thesis that attend the NMC, that are male and those that were recruited out of the potential NMC and estimated national populations. In addition, participant's frequency of physiotherapy (median and range) is included, which as stated previously, is typically dependant on the severity of condition and locality to The NMC. Note: This thesis has only recruited adults that visit the NMC at least once a month as to improve reliability of measures.

In terms of co-morbidities, of the MD participants, 4 participants were prescribed with beta blockers, all of which had BMD. ACE inhibitors were used by 3 of 18 with BMD, 2 of 13 with LGMD, and 2 of 14 with FSHD. There was no use of ACE inhibitors or beta-blockers within the DMD participants. Regarding cardiac dysfunction, 2 of those with BMD had previously been diagnosed with cardiac myopathy. There is no evidence that these medications or co-morbidities would impact the outcome measures reported in the present thesis.

Table 3.1. Participant Recruitment.

	DMD	**BMD**	**LGMD**	**FSHD**
NMC Total	20	44	55	64
NMC Total Males	20	44	24	31
Recruited	16	18	13	14
% of possible recruits	80%	41%	54%	45%
Estimated % of National Population	1.3%	0.75%	1.8%	1.4%
Physiotherapy Frequency (Monthly Visits)	3 (1-4)	2 (1-2)	2 (1-2)	2 (1-2)

Table 3.1. NMC = The Neuromuscular Centre; DMD = Duchenne Muscular Dystrohpy; BMD = Beckers Muscular Dystrophy; LMD = Limb-Girdle Muscular Dystrophy; FSHD = Facioscapulohumeral.

3.1.3 Age Differences

Given the condition onset from birth in DMD and in adulthood in FSHD (Emery, 2002), differences were expected between MD groups and CTRL. Therefore sub-group analysis was

performed on the primary outcome measure (KEMVC), CTRL participants were split into Young (aged 18-30, n= 8) and Old (aged 31-55, n= 8) subgroups, so they matched with DMD and FSHD, respectively. As this approach provided the same statistical outcomes as a combined CTRL group, only comparisons for a combined CTRL are presented.

3.1.4 Control Participants

As stated above, this thesis has utilised a single CTRL group for all of its cross-sectional comparisons, therefore it is important to identify if the CTRL group is reflective of the larger population. Therefore, using the main outcome measure that has been utilised through this thesis of KEMVC, the coefficient of variation of our CTRL KEMVC was 34%, which is comparative with the normative database for quantitative muscle testing (QMT)((Hogrel et al., 2007); n = 122, CV = 29%, mean difference = 4.3 N.m), and therefore deemed reflective of the larger population.

3.1.5 Participant Information and Ethical Approval

All MD participants were recruited from, and tested at, The Neuromuscular Centre (Winsford, UK). CTRL were tested at Manchester Metropolitan University, Cheshire Campus (Crewe, UK). Only males were recruited to allow cross-condition comparison, aged 18-55. CTRL participants were self-reported as being recreationally active (undertaking less than 2 hours of recreational physical activity per week), however were not undertaking any structured training programme. Similarly, no MD participants were taking part in a structured training programme, however all were receiving weekly, bi-weekly or monthly physiotherapy treatment, consisting of passive stretching, along with access to low intensity cardiovascular exercise equipment**.** Ethical approval was obtained through the Department of Exercise and Sport Science local Ethics Committee, and all participants signed informed consent forms

prior to participation (Appendix 3). All procedures complied with the World Medical Association Declaration of Helsinki (World Medical, 2013).

3.2 Research Design

This section provides an overview of the variables reported in each chapter, and how the testing was conducted, these are presented in Figure 3.1. Further identification of variables and methodologies are made in 3.5 Measures. An overview of participants relative to each Chapter is presented in Figure 3.1. The variables for each Chapter are identified below, and variations in sample sizes explained.

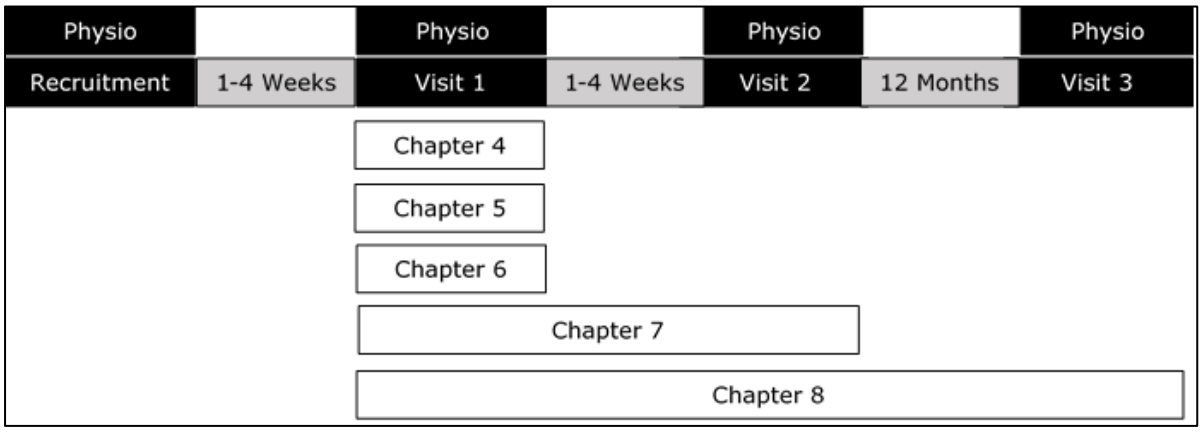

Figure 3.1 Overview of data colleciton and relevant chapters. From left to right, the possible commitments and tests made by participants is identified, with data collection sessions at visit 1, 2 and 3.

Participants testing was aligned with participant's subsequent physiotherapy sessions. During Visit 1, variables for participant characteristics of body mass (BM), height, body fat % and LBM that are used to describe participants in every chapter, were recorded.

Variables associated with Chapter 4 of GM ACSA, PFMVC and KEMVC were measured during Visit 1. Measures of PA reported in Chapter 4 were administered during visit 1 through the use of a wrist-worn accelerometer, and was returned during Visit 2. Reliability measures

reported in Chapter 4 were from repeat measures during Visit 2 of PFMVC and KEMVC. This chapter uses all 4 classifications of MD. One DMD participant refused to wear the wrist-worn accelerometer, therefore none of his data was used during this chapter, however in non-PA related chapters, this data was used in subsequent chapters.

Chapter 5 consists of the KEMVC measured during Visit 1, and questionnaires administered during Visit 1. Some participants took the questionnaires home with them following Visit 1, and returned them during Visit 2. Due to the severe upper limb impairments associated with DMD, the principal investigator would tick the boxes chosen on questionnaires for participants. This chapter uses all 4 classifications of MD, however one participant with DMD and one with LGMD did not return their questionnaires, and were therefore not included in this chapter.

Chapter 6 consisted of RoM and Stiffness measures of participants, these were measured during Visit 1. PFMVC reported in Chapter 4 is also used in this chapter. Reliability measures were reported from repeated measures from Visit 2. This chapter uses all 4 classifications of MD, however technical difficulties with the electro-goniometer and its outputs/readings reduced some participant numbers in BMD, LGMD and FSHD.

Chapter 7 uses a prospective cohort design, whereby participants RoM, Stiffness and PFMVC from Visit 1 are repeated during Visit 2 to calculate Minimal Detectable Change (MDC). These variables were included for analysis following their differences and associations presented in Chapter 6. Participants would be tested for pre-physio measures, undergo a standard physiotherapy session, before repeating the testing measures. Effectiveness of physiotherapy is determined by statistical analysis and differences greater than MDC. Only DMD participants were reported for the acute responses to Physiotherapy. Due to the severe lower limb

impairment in DMD, it was deemed that by only including DMD participants, the principal investigator could assess specifically the intervention of Physiotherapy. Other forms of MD, which may contain ambulant individuals, could influence the stiffness properties of the lower limb dependant on the extent of PA achieved prior to their physiotherapy session.

Chapter 8 is a repeated measures design using the participant characteristics, PFMVC, KEMVC and PA from visit 1, and those participants that were still available and willing to participate in a 12 month follow up. Only DMD and BMD participants were utilised for this Chapter, due to the similarities of their genetic impairment, and the typically linear progression of their conditions. Of the participants that completed all baseline testing during Visit 1, all DMD participants were tested at Visit 3 (12 months). While 12/18 BMD participants from baseline testing were available or willing to participate in Visit 3 testing (12 months). In addition, ROM measures were not recorded at 12 months due to technical issues with the electro-goniometer.

Please note, all data collection, data analysis and statistical analysis was performed by the principal investigator.

Table 3.2. Recruited participants utilised in each Chapter

	DMD	BMD	LGMD	FSHD	CTRL
Total Recruited	16	18	13	14	16
Chapter 4	15	18	13	14	16
Chapter 5	15	18	12	14	16
Chapter 6	16	17	10	13	16
Chapter 7	14	-	-	-	-
Chapter 8	15	12	-	-	-

3.2.1 Protocol

All participants completed the following testing during Visit 1, MD participants completed testing prior to their physiotherapy session. The testing protocol was completed in all participants using the same equipment, with the exception of seated scales for BM measures in non-ambulatory MD participants. Due to the high level of whole-body contractures present in some participants, testing was designed for the most severely affected participants to be tested in their own power-wheelchair, with all other participants then assessed in a seated position to ensure consistency. Bioelectrical Impedance (BIA) (Bodystat 1500, Bodystat Ltd., United Kingdom) and anthropometric measures were performed first, followed by B-mode ultrasound measures of the GM (MyLabGamma Portable Ultrasound, Esaote Biomedica, Genoa, Italy). Ultrasound recordings were taken of the participants' self-reported dominant leg. If a participant was unable to distinguish a dominant leg, the right leg was measured. Goniometry assessment of ROM, mechanical properties and displacement through ROM were assessed on the self-reported dominant leg using an electro-goniometer (K100, Biometrics Ltd, UK) and the above-mentioned ultrasound. Quantitative muscle strength was then taken from the self-reported dominant leg using a load cell (Zemic, Eten-Leur, Netherlands) for

PFMVC, followed by KEMVC. Participants then performed a maximal handgrip strength test with their dominant hand. Those MD participants that were capable and confident then completed a 10 m walk. Following completion of physical measures, a wrist-worn accelerometer was attached to the wrist of the self-reported dominant arm, and worn for seven consecutive days (GENEActiv, Cambridge, United Kingdom). In addition, participants were given a pack of health related questionnaires to complete (participants were instructed to return both the questionnaires and accelerometer at their next physiotherapy appointment). For the questionnaires, the principal investigator was available to answer any queries, however participants were allowed to take the questionnaires home to reduce time commitments. In the case of DMD participants, the principal investigator was available to assist with completion, given their severe physical limitations.

Only MD participants performed Visit 2. Visit 2 consisted of all physical measures reported above, with the exception of 10 m walk, and were completed Pre-Physio and Post-Physio. Visit 3 (12 months follow up) completed the physical measures of participant characteristics, PFMVC, KEMVC and PA.

3.3 Measures

3.3.1 Anthropometry

CTRL participants' BM was measured by digital scales (Seca model 873, Seca, Germany). Alternatively, all MD participants were weighed in a digital seated scales system (6875, Detecto, Webb City, Mo, USA). Slings, shoes, splints etc. were weighed separately and subtracted from the gross weight. All participants' height was calculated as point-to-point of arm span (index finger, elbow, shoulder and across midline) to replicate the method used on non-ambulatory participants, consistent with previous MD research (Morse, 2016; Morse et al., 2018; Morse et al., 2015). A correction of 3.5% was applied to the raw data, consistent

with regression data from Caucasian males in order to account for the known discrepancy between height and arm span measures (Reeves et al., 1996).

3.3.2 Body Composition

Body composition measures of fat and lean LBM were measured using BIA in a fasted state, with adhesive electrodes placed on the right hand and foot. Two distal electrodes were placed on the dorsal surfaces of the metatarsals and metacarpals, and two proximal electrodes were placed between the medial and lateral malleoli of the right ankle, and between the styloid processes of the right ulna and radius. BIA has been commonly used as a quicker, cheaper and more easily accessible alternative to other body composition measures, such as Dual-Energy X-Ray Absorptiometry (DEXA). BIA has been shown to be valid and reliable in comparison to DEXA in adults of healthy weight (r=0.99) (Okasora et al., 1999) and in overweight populations (r=0.78) (Sun et al., 2005). In addition, BIA has been promoted as a measure for change in fat and LBM over time in a dystrophic population (Mok et al., 2010).

LBM was determined by the following equation:

$$LBM\ (Kg) = Body\ Mass\ (Kg) - Fat\ Mass\ (Kg)$$

Body Mass Index (BMI) was calculated using the following equation (McCabe et al., 2013):

$$BMI\ (\frac{Kg}{m^2}) = Body\ Mass\ (Kg) \div Height^2 (m^2)$$

3.3.3 Muscle Morphology

The same B-mode real-time ultrasound (MyLab Gamma; Esaote, Reading, Berks, UK) with a 7.5-MHz linear array probe was used to complete all measurements of Tibia Length (L^{Tibia}), Achilles Tendon Length (L^{Tendon}) and L^{GM}. All measures took place with the participant seated, with knee and hip angles maintained at 90°. Non-ambulant participants remained seated within their manual/power wheelchair. All participants were measured with ankle angle as

close to 0° (neutral position) as possible, however, not all participants' ankles were able to be mechanically moved into a neutral position, with ankles typically in a plantar-flexed position due to contractures, and so measures were taken from as close to neutral position as possible.

3.3.3.1 Muscle-Tendon Unit Length

L^{Tibia} was measured using a tape over the skin surface following identification of the medial condyle and medial malleolus. L^{GM} was measured using tape over the skin surface following identification of the visible origin of the GM at the posterior aspect of the femur to the distal formation of the MTJ by use of sagittal plane ultrasonography. L^{Tendon} was measured as the distance from the GM MTJ to the insertion of the Achilles tendon into the calcaneus. MTU length (L^{MTU}) was determined by the sum of L^{GM} and L^{Tendon}.

3.3.3.2 GM ACSA

GM ACSA was measured using transverse ultrasound scans (7.5-MHz linear array probe) at 50% of muscle length, consistent with the muscle length at which the largest ACSA occurs (Fukunaga et al., 1992). Muscle length was measured with a tape measure over the skin surface, following identification of the visible origin of the GM at the posterior aspect of the femur to the distal formation of the MTJ through ultrasonography.

Echoabsorptive tape (Transpore, 3M, USA) was used to project shadows on the ultrasound image during recording to provide a positional reference. Strips of tape were placed longitudinally across the GM at 50% of muscle length, at approximately 3 cm intervals. The probe was moved in the transverse plane from the medial to the lateral borders of the muscle while digitally recording. Ultrasound transmission gel (Aquasonic 100, New Jersey, USA) was used to maximise image quality; minimal and consistent pressure was applied to avoid compression of the muscle. Ultrasound was recorded in real time (at 25 frames per second) and stored prior to digitising. Ultrasound recordings were exported into video editing

software (PowerDirector V6; Cyberlink Corporation, Tokyo, Japan), from which still images were captured. Images were captured at intervals consisting of two reference markers, as shown by shadows projected on the muscle from echoabsorptive tape. The entire GM ACSA was then recreated into a single image (Graphic Image Manipulation Program, GIMP Development) using the shadows from echoabsorptive tape, muscle markers and aponeurosis of the muscle. The ACSA was then measured using digitising software (ImageJ 1.45, National Institute of Health, USA). This method of ACSA measurement using ultrasound has been performed previously in dystrophic conditions (Morse et al., 2015; Jacques et al., 2017), and previously reported as a valid (0.998) and reliable (0.999) measure in comparison to magnetic resonance imaging (MRI) (Reeves et al., 2004).

3.3.4 Ankle ROM

An electro-goniometer (K100, Biometrics Ltd, UK) was attached to the self-reported dominant ankle, aligned with anatomical landmarks of the fibula and fifth metatarsal bone, and calibrated using a manual goniometer. The electro-goniometer was displayed in real-time on a laptop to provide feedback by a self-coded program using MyLabView (National Instruments, Berkshire, UK). All participants were tested in a seated position with hip and knee angles at 90°s, a 30 cm block was also placed under the knee of participants, ensuring foot clearance from the ground. For ROM presentation, goniometric data is presented with 0° as a right angle to the tibia, with movement superiorly considered negative, and inferiorly considered positive, relative to 0° (see Figure 5.1). This presentation of ankle angle as positive and negative in consistent with previous work associated with ankle stiffness measurements (Morse, 2011; Morse et al., 2008; Ryan et al., 2008; Mizuno et al., 2013a; Mizuno et al., 2013b).

3.3.4.1 Resting Angle

A single measure of resting angle, defined as the angle in which the ankle rests at naturally without any force applied, was recorded.

3.3.4.2 ROM^{Active}

Two trials were performed for total ROM^{Active}, consisting of the participant moving their foot independently to its maximum ROM, with the principal investigator stabilising the ankle. Participants were instructed to "point your toes towards the floor as much as you can" to identify maximum active plantarflexion (Max PF^{Active}), followed by "point your toes to the sky as much as you can", to identify maximum active DF (Max DF^{Active}). The maximum values were taken as Max DF^{Active} and Max PF^{Active}, respectively. ROM^{Active} was determined by the absolute sum of Max PF^{Active} and Max DF^{Active}.

3.3.4.3 ROM^{Passive}

To perform ROM^{Passive} assessment the dominant foot of participants was securely fastened to a footplate, with a load cell attached underneath (see Force Measures below), (Note: the footplate was not attached for either Resting Angle or ROM^{Active} measures, as the weight of the footplate could impact resting angle, or the participant's ability to perform ROM^{Active}).

Two trials were performed to identify Max PF^{Passive} and Max DF^{Passive}, with the principal investigator moving the foot through ROM until participant discomfort, with maximal values used for analysis. ROM^{Passive} was determined by the absolute sum of Max PF^{Passive} and Max DF^{Passive}.

Subsequently, two trials of ultrasound and stiffness assessment were then performed (see MTU and GM Stiffness below).

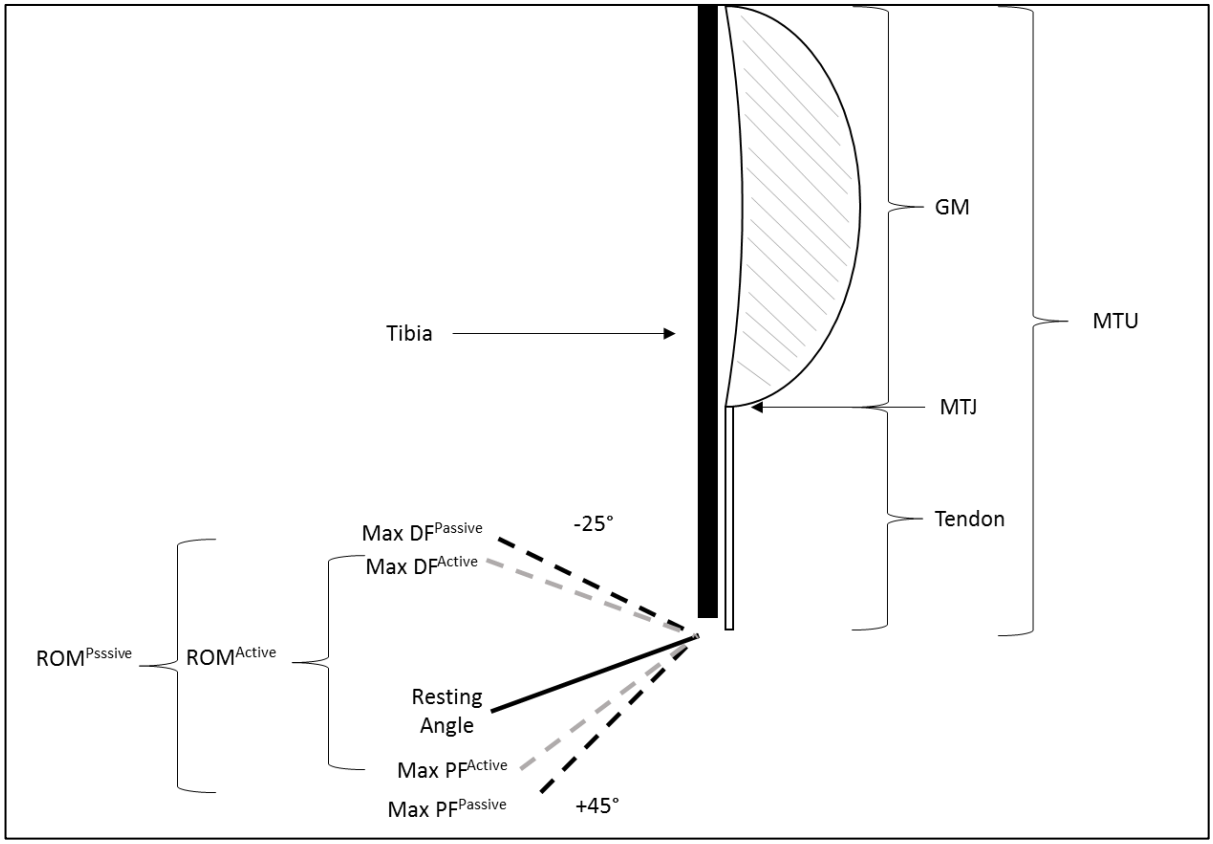

Figure 3.2: Schematic diagram of MTU Morphology and ROM Measures. $ROM^{Passive}$ – Passive Range of Motion; ROM^{Active} – Active Range of Motion; Max $DF^{Passive}$ – Maximum Passive Dorsi-Flexion; Max DF^{Active} – Maximum Active Dorsi-Flexion; Max PF^{Active} – Maximum Active Plantar-Flexion; Max $PF^{Passive}$ – Maximum Passive Plantar-Flexion; GM – Gastrocnemius Medialis; MTJ – Myotendinous Junction; MTU – Muscle-Tendon Unit.

3.3.4.4 Reliability of ROM measurement

Goniometry has been extensively used to monitor ROM in DMD (Archibald and Vignos Jr, 1959; Johnson et al., 1992). In DMD high intra-tester reliability has been reported (ICC= 0.90), however lower reliability has been reported for inter-tester reliability (ICC= 0.73) (Pandya et al., 1985), therefore the Principal Investigator recorded all goniometric assessments. Reliability testing was performed across all four dystrophic conditions, with within-day

reliability performed with 1 minute breaks between trials, while between-day reliability was performed over 2 separate days, separated by 1-4 weeks, to coincide with participants' physiotherapy appointment. The high between-day Intra-Class Correlations (ICC) (See Table 5.1) are testament to the lack of condition progression in the short time period between assessments.

Table 3.3. Intra-Class Correlations of Goniometry

Condition	n	Between-Day ICC		Within-Day ICC	
		$ROM^{Passive}$	ROM^{Active}	$ROM^{Passive}$	ROM^{Active}
DMD	16	.962	.984	.965	.969
BMD	17	.891	.932	.958	.964
LGMD	10	.894	.841	.913	.932
FSHD	13	.901	.912	.924	.949

Table 3.3. Intra-Class Correlations of Goniometry. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD = Facioscapulohumeral Muscular Dystrophy, ICC = Intra-Class Correlations, $ROM^{Passive}$ = Passive range of motion, ROM^{Active} = Active range of motion.

3.3.5 Muscle Properties through RoM

Simultaneous recordings of MTJ Displacement, passive PF torque, and joint angle were recorded for the calculation of MTU and GM stiffness through $ROM^{Passive}$, with one minute breaks between trials. The Principal Investigator moved the participant's foot though $ROM^{Passive}$ from the previously identified Max $PF^{Passive}$ to Max $DF^{Passive}$ at a maximum rate 5°. s^{-1} (Morse et al., 2008), measured by a live feedback system. Measures of MTJ Displacement and Max Passive PF Torque are presented relative to the resting angle, comparable with previous methods of GM stiffness in CTRLs (Blazevich et al., 2014), and consistent with methods used in cerebral palsy where participants feet typically remain in PF (Hussain, 2013).

3.3.5.1 MTJ Displacement

During assessment of movement through ROM^{Passive}, B-mode ultrasonography was used to track the distal displacement of the previously identified GM MTJ (See Muscle Morphology). The GM was chosen for analysis as it contributes significantly more to the contractile area of the triceps surae than the Gastrocnemius Lateralis (26% vs 12%, respectively) (Albracht et al., 2008), hence contributes more to the passive properties of DF. In addition, although the Soleus contributes more (62%) to PFMVC, the deeper nature of the Soleus, along with the degradation of muscle tissue impairs ultrasound image quality (Jacques et al., 2017; Morse et al., 2015), making it difficult to accurately track in MD. Furthermore, tracking of the soleus requires participants to be laid prone, which the DMD participants would be unable to do. The ultrasound was time-locked with force and goniometer outputs. MTJ displacement was measured relative to an acoustically reflective marker (a thin strip of micro-pore tape) on the skin proximal to the MTJ, consistent with techniques used previously (Maganaris, 2005). Images were recorded online from Max PF^{Passive} to Max DF^{Passive} and analysed offline every 5° from resting angle to Max DF^{Passive}, using digitising software (ImageJ 1.45, National Institute of Health, USA).

3.3.5.2 Max Passive PF Torque

Max Passive PF torque was calculated based on force measures recorded using a load cell attached underneath the footplate. The force produced was digitized using an analogue-to-digital converter and displayed in real-time using a self-coded program using MyLabView (National Instruments, Berkshire, UK). Force (N) was converted to moment (N.m) by multiplying the force measurement by the moment arm, from the axis of rotation (ankle) to the point of the load cell on the footplate. Force measures were displayed in real-time, but analysed offline. Due to the severe level of contractures and difficulties with body mechanics, all strength testing protocols were designed for the most severely physically limited

participants, and replicated across all conditions and participants. The load cell was calibrated prior to every testing session in 500g increments, up to 5kg.

Due to some passive PF torque being recorded even when at rest, attributed to the mass of foot and limitations of ROM, Max Passive PF torque was normalised to 0 N.m from the point of resting angle, and measured from this point to Max $DF^{Passive}$. Two trials were performed with the Max Passive PF Torque taken for analysis. If more than 5% difference was found between the two trials for Max Passive PF Torque, a third trial was performed. Similar methods of passive PF torque assessment have been used previously in other clinical conditions (Rao et al., 2006).

3.3.5.3 Stiffness Calculations

MTU and GM stiffness are calculated as below (Morse, 2011; Morse et al., 2008):

MTU stiffness ($N.m.deg^{-1}$) = Max Passive PF Torque (N.m)/ Ankle Angle (deg)

GM stiffness ($N.m.cm^{-1}$) = Max Passive PF Torque (N.m)/MTJ Displacement (cm)

3.3.6 Strength

Due to the severe level of contractures and difficulties with body mechanics, all strength testing protocols were designed for the most severe participants, and replicated across all conditions and participants. Isometric PFMVC and KEMVC force was recorded using a load cell with the participants in a seated position. The load cell was calibrated prior to every strength testing session. Three trials were performed, with extended breaks of 1 minute between trials due to the increased fatigue associated with MD (Sharma et al., 1995). The highest measure of the three trials was used for analysis. The force produced was digitized using an analog-to-digital converter, displayed by a self-displayed and coded program using MyLabView (National Instruments, Berkshire, UK). Force (N) was converted to moment (N·m) by

multiplying the force measurement by the moment arm from the axis of rotation (knee or ankle) to the point of force measurement (the strap height on the shin, or ball of the foot). PFMVC and KEMVC measures have been presented as torque (N.m) and normalised to BM (N.m/Kg) and presented as KEMVC/BM and PFMVC/BM respectively, while PFMVC is also normalised to GM ACSA (N.m/cm^2) and presented as PFMVC/ACSA.

3.3.6.1 MVC Protocol

All MVC measures took place with the participant seated, with knee and hip angles maintained at 90°. Non-ambulant participants remained seated within their manual/power wheelchair. For KEMVC, straps were used to limit hip flexion during contractions. A strap was securely fastened around ankle and attached perpendicularly to the load cell, which was securely fastened to a weighted support bar. The strap length was shortened until the strap was taut between the load cell and limb, while maintaining limb position. All participants were verbally encouraged throughout their maximal effort.

All participants PFMVC was measured with ankle angle at 0° (neutral position), however, not all participants' ankles were able to be mechanically moved into a neutral position, with equinus deformity common in MD (Williams et al., 1984), and so measures were taken from as close to neutral position as possible. The participants' foot was attached to a footplate, with the load cell attached underneath. The Principal Investigator produced the resistive force to ensure a static/isometric contraction occurred during MVC. Plantar-flexion forces were normalised for gravity.

3.3.6.2 MVC Reliability

Similar techniques to those used within this chapter have been common within neuromuscular research. The KEMVC protocol is similar to Quantitative Muscle Testing, and has been previously used within both clinical and non-clinical populations (Brussock et al.,

1992; Hogrel et al., 2007; Narici et al., 1996). The plantar-flexion measures are restricted by the mechanical limitations previously mentioned within these conditions, namely capacity the put the leg into full extension due to contractures and remain self-supported; however similar techniques using a non-mechanical resistive force are common in dystrophic research (Willis et al., 2013; McDonald et al., 2013). Reliability testing was performed across all four dystrophic conditions, with within-day reliability performed with 1 minute breaks between trials, while between-day reliability was performed over 2 separate days, separated by 1-4 weeks, to coincide with participants' physiotherapy appointment. Intra-Class Correlations (ICC) (See Table 3.1) showed strong reliability for between-day and within-day reliability across all conditions for KEMVC and PFMVC, and were in fact comparative or even stronger than ICCs in previous quantitative muscle assessment studies (Personius et al., 1994; Escolar et al., 2001; Lewelt et al., 2015).

Table 3.4 Intra-Class Coefficients for Muscle Strength

Condition	**n**	**Between-Day ICC**		**Within-Day ICC**	
		Plantar-Flexion	Knee Extension	Plantar-Flexion	Knee Extension
DMD	15	0.984	0.987	0.985	0.991
BMD	18	0.832	0.991	0.911	0.992
LGMD	13	0.946	0.985	0.921	0.980
FSHD	14	0.921	0.956	0.934	0.973

Intra-Class Correlations for muscle strength in dystrophic conditions. DMD – Duchenne Muscular Dystrophy; BMD – Beckers Muscular Dystrophy; LGMD – Limb-Girdle Muscular Dystrophy; FSHD – Facioscapulohumeral Dystrophy.

3.3.7 Handgrip

A digital handgrip dynamometer (Jamar plus, Patterson Medical, USA) was used to assess grip strength. Of the participants able to produce a measureable grip strength (three DMD participants produced 0 kg grip strength), three maximal attempts were performed. Measures were taken in a seated position for all participants, on their self-reported dominant hand,

with the arm in an extended position to the side of the body. Extended one-minute rest periods were allowed between trials due to the previously mentioned high fatigability of these conditions.

3.3.8 10m Walk Test

A 10m walk test was performed by 20 out of 24 ambulant participants (8 BMD, 2 LGMD and 10 FSHD). The 10m walk was performed on an even, carpeted surface, and is a common measure of function within neuromuscular conditions (McDonald et al., 2013; Fowler et al., 2017). All participants started in a standing position and were instructed to walk as quickly and safely as they could, with the time recorded from the point of "Go" from the Principal Investigator, to the point of crossing the finish line. Walking aids were permitted if required. Given the limited numbers, these participants were pooled for analysis upon 10m walk time. Please note that the 10m walk time was used only for MD participants, this is a standard functional measure relevant to clinical groups, and was therefore not measured in CTRL.

3.3.9 Physical Activity

Daily PA was monitored over a consecutive 7-day period using a wrist-worn tri-axial accelerometer (GENEActiv, Kimbolton, Cambs, United Kingdom). Wrist worn accelerometers have previously been recommended as the best location for accelerometers for wheelchair users (Nightingale et al., 2015). Furthermore, accelerometer attachment of mid-thigh was trialled on one participant, however had to be removed due to being uncomfortable once back their wheelchair. In addition, this thesis is focused on monitoring activity, rather than sitting time, therefor wrist-worn accelerometers other hip or mid-thigh accelerometer was deemed acceptable. Monitors were worn for 24 hours a day on the preferred wrist of participants and worn continuously for 7 days, which was deemed the minimum wear time (Dillon et al., 2016). Monitors remained on during sleep, with no participants, or collected

data, suggesting monitors removed during sleep, or during the 7 days of data collection. Monitors were initialised to collect data at 100 Hz and acceleration values, recorded in "g's", and recorded continuously on each axis (x, y, and z). Recorded total activity time has been previously validated against doubly labelled water (van Hees et al., 2011). In addition, GENEActiv validation studies for both PA and SB have shown strong correlations (Pearson's r=0.79-0.98) (Phillips et al., 2013; Esliger et al., 2011).

Once wrist-worn monitors were returned post 7-day period, data was downloaded from monitors into .bin files and converted into 60s epoch .csv files using the GENEActiv PC Software (Version 2.1). 60s epoch data files were entered in an open source Excel macro (v2, Activinsights Ltd.) (Esliger et al., 2011), which classified activity as sedentary (SB), light, moderate or vigorous intensity, dependant on the physical characteristics of participant age, height and weight. The PA intensity thresholds used within the macro were not designed for adults with MD, therefore rather than incorrectly allocating PA to intensity domains, activity will be presented as time as sedentary or total time spent physically active (TPA). TPA, the sum of light, moderate and vigorous PA time, is presented as average daily minutes (TPA^{mins}), while SB is presented as percentage of waking hours (SB%). Both SB% and TPA^{mins} will be used for comparisons, as well as correlations and regression analysis.

3.3.10 Questionnaires

3.3.10.1 Quality of Life

All participants completed the SF-36v2 questionnaire (Appendix 4), a reliable and validated measure, with eight domains of QoL (Ware Jr and Sherbourne, 1992; Jenkinson et al., 1999). The constructs for the domains of QoL are Physical Functioning, Role-Functioning Physical, Role-Functioning Emotional, Social Functioning, Bodily Pain, Mental Health, Vitality and General Health (Ware et al., 2008). All measures are scored out of 100, with higher scores

representative of better health, better function and less pain. The SF-36v2 has been used and validated extensively in the general population; however, it has also been used extensively in Dystrophic populations (Simonds et al., 1998; Padua et al., 2009; Abresch et al., 2002; Kohler et al., 2005). In addition to the eight domains within the SF-36v2, data is also presented as Total Mental and Total Physical component scores, and SF6D, a total mean score derived from a selection of SF-36v2 items. All data was analysed using Health Outcomes Scoring Software 4.5 (QualityMetric Health Outcomes™, Lincoln, United Kingdom). Furthermore, the SF-36v2 allows for participants perspective on their lives generally, more recent neuromuscular disorder QoL assessments have very specific questions, consisting of "how does your condition affect…." (Vincent et al., 2007). These forms of assessment restrict CTRL comparisons, and similarly require participants to disassociate many aspects of their lives from their condition, which may or may not be affected them.

3.3.10.2 Activities of Daily Living

Activities of Daily Living (ADL) were assessed using the Nottingham Extended ADL Scale (NEADL; Appendix 5), a 22 item based measure of ADL covering four domains of activity (Mobility, Domestic, Kitchen and Leisure). Respondents record what they have actually done over the last few weeks, with possible answers "Not at all", "With help", "On your own with difficulty", or "On your own". To increase sensitivity, scores were allocated using a Likert scale "0-1-2-3" (Sveen et al., 2004; Ho et al., 2001), rather than "0-0-1-1" as typically used, therefore scores ranged from 0-66 with higher scores representing greater independence. The NEADL has been previously validated in other clinical conditions (Gladman et al., 1993; Harwood and Ebrahim, 2002).

3.3.10.3 Fatigue

The Checklist Individual Strength (CIS; Appendix 6) is a 20-item self-report questionnaire originally developed for Chronic Fatigue Syndrome (Vercoulen et al., 1994). The CIS has domains of: Fatigue Severity (8 items), Concentration (5 items) Motivation (4 items) and physical activity level (3 items), as well as Total. Items are scored on a 7-point Likert scale. Higher scores indicate a higher degree of fatigue, concentration problems, reduced motivation or less activity, respectively. Reliability of CIS has been previously reported as good (α= 0.82-0.92) (Vercoulen et al., 1994) and has good discriminate validity (Vercoulen et al., 1999). The Severity subscale of the CIS has been used previously to identify chronic fatigue in adults with FSHD (Kalkman et al., 2005; Voet et al., 2014). Therefore, for the purposes of the present study, while participants completed the whole 20-item questionnaire, only the Fatigue Severity scale (8 items) from the CIS has been used for analysis, and is hereafter referred to as CIS Severity, and is scored out of a possible 56, with scores over 35 deemed representative of chronic fatigue.

3.3.10.4 Pain

A Visual Analog Scale (Pain VAS) of pain was used to quantify the level of pain felt by participants over the 7 days preceding assessment (Appendix 7). VAS is a common method of pain assessment (Price et al., 1983) and used in many conditions (Padua et al., 2009; Douvillez et al.; Moulin et al., 1997). Participants were given a 10cm straight line, with at one end “No Pain”, and the other “Worst Possible Pain”, and instructed to mark where, on average, they felt their pain over the preceding 7 days was on the scale. The mark was then measured and presented as distance (cm) from the “No Pain” end.

3.3.10.5 Self-Efficacy

The General Self Efficacy Scale (Jerusalem and Schwarzer, 1979) is used as a measure of an individual’s perception of their ability to overcome problems and challenges (Appendix 8).

Most Self-Efficacy scales used clinically are rehabilitative, and focussed on improvements or return to physical status, and were deemed invalid for a degenerative muscle condition. Therefore, The General Self Efficacy Scale was used, a scale which focuses on overcoming problems rather than rehabilitation. The General Self Efficacy Scale is a 10-item scale, using a 4-point Likert Scale for each question. Possible responses to questions are: *not at all true* (1), *hardly true* (2), *moderately true* (3), and *exactly true* (4), resulting in a total score between 10 (lowest possible) and 40 (highest possible). High reliability, stability, and construct validity have been confirmed in various previous studies (Leganger et al., 2000; Schwarzer et al., 1999), with strong Crohnbach Alpha levels ranging 0.87-0.95 across different clinical conditions (Luszczynska et al., 2005).

3.3.11 Physiotherapy Intervention

For the Physiotherapy intervention in Chapter 7, all participants received their standard physiotherapy treatment delivered by the same Chartered Physiotherapist with experience in managing long-term muscle conditions. Physiotherapy sessions consisted of 60 minutes of whole-body passive stretches and range of movement exercises. Consistent with participants' standard treatment, particular focus was given to moving muscles and joints to their maximal length and end ROM respectively, with general focus given to typical areas of limited ROM, namely ankles, hips, shoulders and fingers (Bushby et al., 2010). While each individual's treatment would be slightly different to target issues relevant to their own condition progression and presentation, relevant to the outcomes in the present chapter, a minimum of 5 minutes of DF stretching was administered. DF was the focus of the treatment, as limited DF is a recognised feature of DMD (Williams et al., 1984) and consistently limited across adults with DMD (Chapter 5). As this thesis is describing the current "service provision" of physiotherapy, rather than conducting a set number of stretches, it is not possible to outline

in further detail what was completed within each individual session. Normal practice for stretches tends to be limited by the participants' volitional stretch tolerance. Despite the limited guidance for physiotherapists working with neuromuscular disorders, typical practice at The NMC for passive stretches consists of holding stretches at their maximal length for up to 30s, before a release of stretch, and then passively stretch to maximal length again.

3.3.12 Minimal Detectable Change

Consistent with previous research, the author deemed it unethical to deny any participants access to physiotherapy (Hyde et al., 2000), therefore no CTRL group was formed. MDC scores were however, calculated to determine the minimal change required beyond the error of measurements (Haley and Fragala-Pinkham, 2006). MDC was calculated using intra-class correlation coefficients (ICC) and standard error of measurements (SEM) from data collected at baseline and pre-physio (Hoch et al., 2012). MDC scores are presented in relevant tables, intervention changes are only deemed significant if they meet both statistical and MDC criterion. Calculations are as below:

$$SEM = Baseline\ SD\ x\ (\sqrt{1 - ICC})$$

$$MDC = 1.96\ x\ SEM\ x\ \sqrt{2}$$

Please note: adults with DMD are severely impaired (Chapter 4) and all participants use powered-wheelchairs, therefore no internal or external influences are likely to affect ROM, any effect identified in the present chapter is likely a direct result of the physiotherapy received. This is emphasised by the SB% times occupying 98% of their waking hours (Chapter 4).

Furthermore, please note that the principal investigator is aware of minimal clinically important difference (MCID). The use of MCID however for the effectiveness of physiotherapy

was deemed redundant in this case. While MCID may be relevant for conditions whereby a return to function is possible, given the extremely limited ROM in DMD, no possible return to function and a lack of previous data, MCID was not used during this thesis to assess physiotherapy.

Chapter 4

Relationships between muscle size, strength and physical activity in adults with Muscular Dystrophy

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4.1 Abstract

Background

Muscular Dystrophy (MD) is characterised by progressive muscle wasting and weakness, yet, few comparisons to non-MD controls (CTRL) of muscle strength and size in this adult population exist. Physical activity (PA) is promoted to maintain health and muscle strength within MD, however PA reporting in adults with MD is limited to recall data, and its impact on muscle strength is seldom explored.

Methods

This chapter included 76 participants 16 CTRL, 15 Duchenne (DMD), 18 Becker's (BMD), 13 Limb-Girdle (LGMD), 14 Facioscapulohumeral (FSHD)). Body fat (%) and lean body mass (LBM) were measured using bioelectrical-impedance. GM ACSA was determined using B-mode ultrasound. Isometric maximal voluntary contraction (MVC) was assessed during plantar-flexion (PFMVC) and knee extension (KEMVC). Physical activity was measured for seven continuous days using tri-axial accelerometry, and was expressed as daily average minutes being physically active (TPA^{mins}) or average daily percentage of waking hours being sedentary (Sedentary Behaviour). Additionally, 10m walk time was assessed. The Kruskal Wallis test with post-hoc Mann-Whitney U (Least Significant Difference) pairwise comparisons for non-parametric comparisons and one-way analysis of variance (ANOVA), with Tukey's used for post-hoc comparison, for parametric data. Kendall Tau correlations were used to identify associations and Bivariate linear regression were used to identify the best predictor of 10m walk from associated variables.

Results

MD groups had 34-46% higher body fat (%) than CTRL. Only DMD showed differences in LBM with 21-28% less LBM than all other groups. PFMVC and KEMVC were 36-75% and 24-92% lower respectively, in MD groups than CTRL. GM ACSA was 47% and 39% larger in BMD and

LGMD, respectively compared to CTRL. No other group differences in GM ACSA were observed. PFMVC was associated with GM ACSA in DMD (r= 0.429) and CTRL (r= 0.553). All MD groups were 14-38% more sedentary than CTRL groups, while DMD was more sedentary than BMD (14%), LGMD (8%) and FSHD (14%). Sedentary Behaviour was associated with LBM in DMD participants (r= -0.446). TPA^{mins} was associated with KEMVC (r= 0.540) in BMD participants, while TPA^{mins} was also the best predictor of 10m walk time (R^2= 0.540) in ambulant participants, revealed by multiple linear regression.

Conclusions

The data from this chapter showed impaired muscle strength in adults with MD and impaired 10m walking time, in ambulant adults with MD. These observations of weakness and 10m walk time were associated with lower levels of TPA in adults with MD. In addition, higher levels of sedentary behaviour were associated with reduced LBM in DMD. These findings suggest a need for investigations into patterns of physical activity behaviour, and relevant interventions to reduce Sedentary Behaviour and encourage PA in adults with MD regardless of impairment severity.

4.2 Introduction

Relationships between muscle size and strength have long been recognised and reported in healthy and clinical populations (Fukunaga et al., 2001; Visser et al., 2000; Hussain et al., 2014). Similarly, the importance of PA and exercise to maintain strength and health is commonly recognised (Goodpaster et al., 2006; Lauretani et al., 2003), these relationships however, have received little or no attention in adults with MD. Where reported in children, the applicability to adults may be limited due to the degenerative/heterogeneous nature of some classifications of MD (Huml, 2015). Despite an increasing volume of research supporting exercise interventions to maintain muscle function within this clinical population (Sveen et al., 2008; Van der Kooi et al., 2004), basic understanding of the relationship between muscle structure/function, and habitual levels of PA in adults with MD remains largely unexplored (Jimenez-Moreno et al., 2017).

Decreased muscle strength has long been recognised within MD and attributed to progressive muscle wasting (Akima et al., 2012; Skalsky et al., 2008; Skalsky et al., 2009). Lower limb strength comparisons between adults with MD and age-matched CTRL have been made in adults with BMD (Løkken et al., 2016), LGMD (Løkken et al., 2016) and FSHD (Skalsky et al., 2008; Bachasson et al., 2014). Of these comparisons, lower KEMVC was attributed to smaller lean mass in the KEMVC muscle group in FSHD (Skalsky et al., 2008). While Løkken et al. (2016) showed PFMVC was associated with cross-sectional area in adults with LGMD. Decreased muscle strength compared to CTRL has been reported in children and adolescents with DMD (Mathur et al., 2010; Akima et al., 2012). In children with DMD, pseudohypertrophy is evident, due to the inflammatory process associated with muscle degradation, resulting in apparent increased calf size compared to age-matched CTRL, however no relative increase in strength (Jones et al., 1983; Deconinck and Dan, 2007). The relationship between cross sectional area

with muscle strength remains unexplored in adults with DMD however, with Morse et al. (2015) reporting decreased cross-sectional area of the GM compared to CTRL, suggesting an end of pseudohypertrophy in adulthood, and muscle size possibly becoming more representative of muscle strength.

Typically, in healthy adult populations, a combination of high habitual PA and medium intensity planned exercise sessions are recommended, in order to maintain and/or improve health, and muscle strength (Warburton et al., 2006; Nelson et al., 2007). Furthermore, within ageing populations, where sarcopenia and muscular atrophy can become evident, PA measures have been positively associated with muscle strength and functional measures (Morie et al., 2010). Similarly, Foong et al. (2015) reported a positive association between PA intensity and both, lower limb strength and lean mass in elderly participants. PA is promoted as a measure to maintain muscle mass and function within MD (Muscular Dystrophy Campaign, 2014). Jimenez-Moreno et al. (2017) however, recently presented a systematic review of habitual PA within neuromuscular disorders, highlighting the distinct lack of PA data currently reported. Subjective recall methods have been primarily used in MD research, namely the BPAQ (MD) (Morse, 2016; Jacques et al., 2017), Baecke Physical Activity Questionnaire (DMD) (Hawker et al., 2005) and a self-developed physical activity questionnaire (DMD) (Heutinck et al., 2015). Objective measures of PA levels in DMD include step count activity (McDonald et al., 2005; Davidson et al., 2015), accelerometry (Jeannet et al., 2011) and doubly labelled water (Elliott et al., 2015), but have only been used with children. Thus, all current research has shown reduced PA levels in MD compared to healthy CTRL, however, only two of the above mentioned papers have measured PA in adults with MD, both of which used recall methods, which lack objectivity (Jacques et al., 2017; Morse,

2016). Recall methods have been shown previously to over-estimate PA, and under-estimate SB (Dyrstad et al., 2014).

In MD, PA may help to maintain muscle mass and strength, conversely, SB is likely to accelerate muscle atrophy through disuse, as well as promote other associated health risks such as increased fat mass, diabetes and heart disease (Shields and Tremblay, 2008; Tremblay et al., 2010; Dempsey et al., 2014; Wullems et al., 2016). Despite the lack of current knowledge and understanding of PA in MD, the importance of exercise and interventions are becoming more and more apparent within MD. Morse et al. (2016) highlighted the strong associations between bone health and lifetime PA in MD. While MD populations have also shown physiological improvements following aerobic exercise interventions (Sveen et al., 2008). Ferguson et al. (2016) showed increased PA levels, through an aerobic training plan, decelerated muscle fat infiltration in adults with FSHD. Moreover, Jansen et al. (2013) showed assisted bicycle training delays functional deterioration in boys with DMD. Further understanding of the habitual PA of adults with MD, along with its relationships with other functional measures, may enhance and specify future interventions.

This chapter aims to: 1) to investigate the relationship between muscle strength and size and 2) establish the relationship between muscle size and strength with objective measures of physical activity, with implications for the maintenance of muscle function in MD.

This chapter hypothesises that measures of KEMVC and PFMVC in MD will appear lower than CTRL, and DMD will be lower than all other MD. PA will similarly be lower in MD than CTRL, and lower in DMD than the other MD. GM ACSA will be associated with PFMVC in BMD and DMD. PA and SB% will be consistently associated with measures of LBM, PFMVC and KEMVC in FSHD, BMD and LGMD.

4.3 Methods

For full details of methods see Chapter 3, in brief: this chapter included 76 participants (16 CTRL, 15 DMD, 18 BMD, 13 LGMD, 14 FSHD). Body fat (%) and LBM were measured using bioelectrical-impedance. GM ACSA was determined using B-mode ultrasound. PFMVC and KEMVC were assessed using methods replicative of QMT. PA was measured for seven continuous days using tri-axial accelerometry, and was expressed as daily average minutes being physically active (TPA^{mins}) or average daily percentage of waking hours being sedentary (Sedentary Behaviour). Additionally, 10m walk time was assessed.

4.3.1 Statistical Analyses

All analyses were performed using IBM Statistics 21 software. The critical level of statistical significance was set at 5%. Tests for parametricity (Shapiro-Wilks and Levenes) were performed upon all variables. All data, except for height and LBM, was non-parametric. Reliability of muscle strength measurements (KEMVC and PFMVC) within and between day was calculated using Intraclass Correlation Coefficients (absolute agreement) within the MD groups (See Table 3.1). The Kruskal Wallis test was used to compare between groups, with post-hoc Mann-Whitney U (Least Significant Difference) pairwise comparisons used where appropriate. Height and LBM was compared between groups using a one-way ANOVA, and Tukey's used for post-hoc comparison. Kendall Tau correlations were used to identify associations of anthropometric variables, muscle size, muscle strength and physical activity. Significant associations with age were identified for KEMVC, KEMVC/BM and PFMBC/BM, therefore ANCOVAs were performed to determine whether differences remained when age was controlled for. Bivariate linear regression were used to identify the best predictor of 10m walk from muscle strength measures and TPA^{mins}. Multiple linear regressions were used when two or more variables were associated. Post Hoc effect size was determined by Phi, using

PFMVC, KEMVC and TPA^{mins}, with moderate-strong effect sizes shown (Phi = 0.75-0.85). Where relevant, comparisons are presented with P values, and the relative difference (%) from a named experimental group.

4.4 Results

4.4.1 Demographic, anthropometric and body composition measures

DMD participants were younger than those with BMD (43%, P<0.001), LGMD (44%, P<0.001), FSHD (49%, P<0.001) and CTRL (32%, P=0.013) (Table 4.1). Furthermore, CTRL were younger than FSHD (25%, P=0.021) (Table 4.1). No other differences were found between groups for age (P>0.05). DMD participants were lighter than BMD (15%, P=0.032), LGMD (25%, P<0.001) and FSHD (15%, P=0.029) participants, while LGMD participants were heavier than CTRL (19%, P=0.012) (Table 4.1). There were no differences in stature between any groups (P>0.05).

No differences were found between groups for BMI (P>0.05, Table 3.2). DMD (45%, P<0.001), BMD (38%, P<0.001), LGMD (56%, P<0.001) and FSHD (34%, P=0.002) participants had higher body fat% than CTRL participants (Table 3.2). DMD participants had less LBM compared to BMD (21%, P=0.001), LGMD (26%, P<.001), FSHD (22%, P=0.002) and CTRL (28%, P<0.001) participants (Table 3.2). No other differences were found between groups for LBM (P>0.05).

BMD GM ACSA was larger than FSHD (40%, P=0.039) and CTRL (47%, P=0.001) participants, while LGMD participants' GM ACSA was larger than CTRL (39%, P=0.015) participants (Table 4.1). No other differences were found between groups for muscle size (P>0.05).

Table 4.1 Participant Characteristics and Anthropometrics

	DMD	BMD	LGMD	FSHD	CTRL
n	15	18	13	14	16
Ambulant	0/15	10/18	4/13	10/14	16/16
Age (years)	24.2 (6.1)^{B,LG,F}	42.4 (13.5)	43.1 (124)	47.1 (11.1)^{C}	35.4 (12.7)
Mass (Kg)	73.1 (14.6)^{B,LG,F}	86.5 (20.3)	96.9 (17.3)^{C}	86.0 (11.2)	81.1 (18.2)
Stature (cm)	172.0 (4.3)	177.4 (6.0)	179.5 (6.9)	178.6 (8.1)	177.5 (9.3)
BMI (Kg/m^2)	25.5 (4.1)	27.3 (6.2)	29.5 (4.8)	26.6 (3.4)	25.5 (3.7)
Body Fat (%)	33.3 (6.7)^{C}	29.2 (10.0)^{C}	33.7 (4.7)^{C}	27.6 (7.3)^{C}	18.2 (4.5)
Lean Body Mass (Kg)	47.6 (7.7)^{B,LG,F,C}	60.0 (9.1)	64.1 (9.3)	61.0 (8.6)	66.0 (13.2)
GM ACSA (cm^2)	23.3 (16.5)	27.9 (15.9)^{C,F}	23.9 (11.0)^{C}	16.6 (4.5)	14.7 (4.5)

Anthropometric measures. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD = Facioscapulohumeral Muscular Dystrophy, CTRL = Control, BMI = Body Mass Index, GM = Gastrocnemius Medialis, ACSA = Anatomical Cross Sectional Area. ^{B} denotes significance from BMD, ^{LG} denotes significance from LGMD, ^{F} denotes significance from FSHD, ^{C} denotes significance from CTRL.

4.4.2 Muscle Strength

CTRL KEMVC was significantly stronger than DMD (92%, P<0.001), BMD (41%, P=0.010) and LGMD (53%, P=0.020) (Table 4.2). DMD participants had weaker KEMVC than BMD (87%, P=0.001), LGMD (87%, P=0.002) and FSHD (90%, P<0.001) (Table 4.2). No differences were found between other groups (P>0.05). All differences between groups remained for KEMVC when age was controlled for by an ANCOVA. DMD participants were also significantly weaker in KEMVC per BM than BMD (86%, P=0.001), LGMD (82%, P=0.001), FSHD (88%, P<0.001) and CTRL (92%, P<0.001) (Table 4.2). While CTRL participants were stronger than BMD (40%, P=0.009) and LGMD (53%, P=0.003) participants in KEMVC/BM (Table 4.2). No other differences between groups were found for KEMVC/BM (P>0.05). When age was controlled for, all differences remained, in addition FSHD were shown as stronger than LGMD (32%, P=0.032) (Table 4.2).

CTRL participants were significantly stronger in PFMVC than DMD (75%, P<0.001), BMD (51%, P<0.001) and LGMD (58%, P<0.001) participants, respectively (Table 4.2). FSHD (62%, P<0.001) and BMD (49%, P=0.007) participants were also stronger than DMD participants (Table 4.2). No other differences were found between conditions (P>0.05). PFMVC/BM in CTRL was significantly stronger than DMD (72%, P<0.001), BMD (53%, P<0.001), LGMD (63%, P<0.001) and FSHD (39%, P=0.006) (Table 4.2). Similarly, FSHD were stronger than DMD (55%, P=0.002) and LGMD (39%, P=0.042) participants for PFMVC/BM. BMD participants greater PFMVC/BM than DMD (42%, P=0.017) participants (Table 4.2). Once age had been controlled for statistically, all differences remained, in addition FSHD were stronger than BMD (23%, P=0.048) for PFMVC/BM (Table 4.2).

CTRL participants had significantly greater PFMVC/ACSA than DMD (80%, P<0.001), BMD (68%, P<0.001), LGMD (72%, P<0.001) and FSHD (40%, P=0.049) participants (Table 4.2). FSHD participants had greater PFMVC/ACSA than DMD (66%, P<0.001), BMD (47%, P=0.009) and LGMD (53%, P=0.005) participants (Table 4.2). No other differences were found between conditions (P>0.05).

4.4.3 Grip Strength

DMD had significantly weaker handgrip strength than BMD (85%, P=0.001), LGMD (85%, P=0.001), FSHD (87%, P<0.001) and CTRL (94%, P<0.001) participants (Table 4.2). Compared to CTRL, grip strength was weaker in BMD (63%, P<0.001), LGMD (63%, P<0.001) and FSHD (55%, P=0.003) groups (Table 4.2). No other differences were found between groups (P>0.05).

Table 4.2 Muscle Strength in Adults with Muscular Dystrophy

	DMD	BMD	LGMD	FSHD	CTRL
KEMVC (N.m)	12.6 (8.8)^{B,LG,F,C}	96.6 (60.0)^{C}	93.5 (56.6)^{C}	123.6 (78.2)	164.6 (55.9)
KEMVC/BM (N.m/Kg)	0.17 (0.1)^{B,LG,F,C}	1.23 (0.9)^{C}	0.97 (0.6)^{F,C}	1.41 (0.8)	2.04 (0.6)
PFMVC (N.m)	16.7 (6.8)^{B,F,C}	32.7 (13.7)^{C}	28.2 (15.4)^{C}	43.8 (20.3)	67.0 (13.1)
PFMVC/BM (N.m/Kg)	0.23 (0.1)^{B,LG,F,C}	0.40 (0.2)^{F,C}	0.31 (0.2)^{F,C}	0.51 (0.2)^{C}	0.84 (0.1)
PFMVC/ACSA (N.m/cm^2)	0.92 (0.5)^{F,C}	1.46 (0.9)^{F,C}	1.29 (0.8)^{F,C}	2.75 (1.3)^{C}	4.58 (0.7)
Handgrip (Kg)	3.0 (3.1)^{B,LG,F,C}	19.5 (14.9)^{C}	19.6 (9.5)^{C}	24.1 (13.2)^{C}	53.5 (10.0)

Strength measures. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD = Facioscapulohumeral Muscular Dystrophy, CTRL = Control, KEMVC = Knee Extension, PFMVC = Plantar-Flexion, N.m = Newton Metres, BM = Body Mass, Kg = Kilograms, ACSA =Anatomical Cross Sectional Area. ^{B} denotes significance from BMD, ^{LG} denotes significance from LGMD, ^{F} denotes significance from FSHD, ^{C} denotes significance from CTRL.

4.4.4 Physical Activity

Participants with DMD displayed higher SB% than BMD (14%, P<0.001), LGMD (8%, P=0.016), FSHD (14%, P<0.001) and CTRL (39%, P<0.001) participants (Table 4.3). Conversely, CTRL had lower SB% than BMD (29%, P<0.001), LGMD (33%, P<0.001) and FSHD (29%, P=0.004) participants (Table 4.3). No other differences were found between conditions for SB% (P>0.05).

DMD participants had lower TPA^{mins} than BMD (88%, P<0.001), LGMD (83%, P=0.010), FSHD (89%, P<0.001) and CTRL (96%, P<0.001) (Table 4.3). Furthermore, BMD (65%, P<0.001), LGMD (76%, P<0.001) and FSHD (64%, P=0.001) had lower TPA^{mins} than CTRL (Table 4.3).

Table 4.3 Physical Activity and 10m Walk time.

	DMD	BMD	LGMD	FSHD	CTRL
TPA^{mins}	13.5 (16.1)^{B,LG,F,C}	115.4 (63.1)^{C}	80.3 (34.6)^{F,C}	117.6 (58.2)^{C}	329.1 (125.0)
SB (%)	97.1 (3.3)^{B,LG,F,C}	83.8 (8.8)^{C}	88.9 (5.4)^{C}	83.1 (6.4)^{C}	59.3 (15.2)
10m Walk (s)*	n/a		11.8 (4.5)		n/a

Physical Activity and 10m Walk. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD = Facioscapulohumeral Muscular Dystrophy, CTRL = Control, TPA^{mins} = Total minutes being physically active, SB = Sedentary Behaviour, m = metre, s = second, * = performed by 20/24 ambulant participants, ^{B} denotes significance from BMD, ^{LG} denotes significance from LGMD, ^{F} denotes significance from FSHD, ^{C} denotes significance from CTRL, * = performed by 20/24 ambulant participants.

4.4.5 Correlations

Age was shown to be significantly associated with measures of PFMVC/BM (r= -0.408, P=0.026), KEMVC (r= -0.343, P=0.048) and KEMVC/BM (r= -0.384, P=0.030) in BMD.

Anthropometric associations with muscle strength revealed significant associations between GM ACSA and PFMVC in CTRL (r= 0.553, P=0.003) and DMD (r= 0.429, P=0.026) participants, respectively. Other conditions showed positive, but non-significant associations between muscle size and PFMVC (P>0.05). No associations were identified between LBM and muscle strength measures in adults with MD (P>0.05).

Sedentary Behaviour was negatively associated with LBM in participants with DMD (r= -0.446, P=0.021), but no other groups. Furthermore, Sedentary Behaviour was negatively associated with KEMVC (r= -0.477, P=0.006) and KEMVC/BM (r= -0.487, P=0.005) in BMD, with other dystrophic groups showing no correlation. Furthermore, TPA^{mins} was associated with KEMVC in BMD (r= 0.407, P=0.020) participants.

Of the participants with the ability to ambulate, 20/24 recorded 10m walk times. Strength measures associated with 10m walk were KEMVC (r= 0.484, P=0.030) KEMVC/BM (r= 0.514, P=0.020), PFMVC (r= 0.502, P=0.024) and PFMVC/BM (r= 0.472, P=0.001). In addition, TPA^{mins} was also associated with 10m walk (r= 0.735, P<0.001). Multiple linear regression identified TPA^{mins} as the greatest predictor of 10m walk time (R^2= 0.540, P<0.001), with all strength measures excluded.

4.5 Discussion

The present chapter showed cross-sectional findings of muscle weakness in adults across four MD classifications, with, as expected a direct relationship between muscle strength and muscle size observed in adults with DMD. In addition, objective measures of PA show increased levels of SB in all dystrophic conditions in comparison to CTRL, particularly within DMD participants who were more sedentary than BMD, LGMD and FSHD participants. Furthermore, relationships were identified between muscle strength, specifically KEMVC, and TPA^{mins} in adults with BMD. Moreover, relationships were also identified between TPA^{mins} and 10m walk times in the 20, cross-condition, participants that completed the functional task.

The present understanding of muscle strength in MD is primarily focussed in DMD paediatric populations (Mathur et al., 2010). Adults with DMD in the present chapter showed KEMVC 92% less than CTRL participants, reflective of the degenerative nature of the condition, with previous paediatric studies reporting KEMVC as 72-86% less than CTRL (Akima et al., 2012; Lott et al., 2014; Mathur et al., 2010; Skalsky et al., 2009; Wokke et al., 2014; Lerario et al., 2012). Similarly, the 75% lower PFMVC reported in the current chapter appears consistent with the progression of the condition, where previous studies have reported PFMVC in paediatric groups as 52-65% lower age-matched CTRL (Lott et al., 2014; Mathur et al., 2010;

Wokke et al., 2014; Vohra et al., 2015). More pronounced muscle weakness is predicted in adults with DMD, however this is likely exacerbated into adulthood by a lack of PA. The relative maintenance of muscle strength of plantar-flexors, compared to knee extensors, is consistent with the classical proximal-distal wasting (Emery, 2002); however may also be influenced by the long term impact of wheelchair-use. There is currently a lack of quality natural history reports using quantative measures of KE or PFMVC in adults with MD (McDonald et al., 2013), which will be described and assessed in Chapter 8.

Despite weakness being a clinical diagnostic tool (McDonald et al., 2013; Griggs et al., 1993), there are limited quantitative measures of muscle strength in adults with MD compared to age matched CTRL. Differences from CTRL in the present chapter are similar to those reported previously. Of the other MDs measured (BMD, LGMD, FSHD), PFMVC in the present study was 42-49% less than CTRL, compared to 48-61% reported in adults with BMD and LGMD (Løkken et al., 2016). Additionally KEMVC in the present study was 25% less than CTRL, compared to 55-58% in previous studies of FSHD (Skalsky et al., 2008; Bachasson et al., 2014). The differences between the present and previous research can be attributed to the heterogeneity of conditions (Wicklund and Kissel, 2014), participant sex differences (present chapter contains all male participants) (Bachasson et al., 2014; Løkken et al., 2016), participants ages (Skalsky et al., 2008; Løkken et al., 2016), differences in strength assessment (Skalsky et al., 2008; Løkken et al., 2016) or condition severity in the participant groups (e.g. 47% non-ambulant, excluding DMD, in the current chapter), with previous research typically all ambulant (Skalsky et al., 2008; Løkken et al., 2016). The presented data can be seen as a comparison to previously reported lower limb muscle strength in Figure 4.1. The present data is particularly novel in the objective assessment of SB and PA as contributing factors to the

differences between groups and participants with MD.

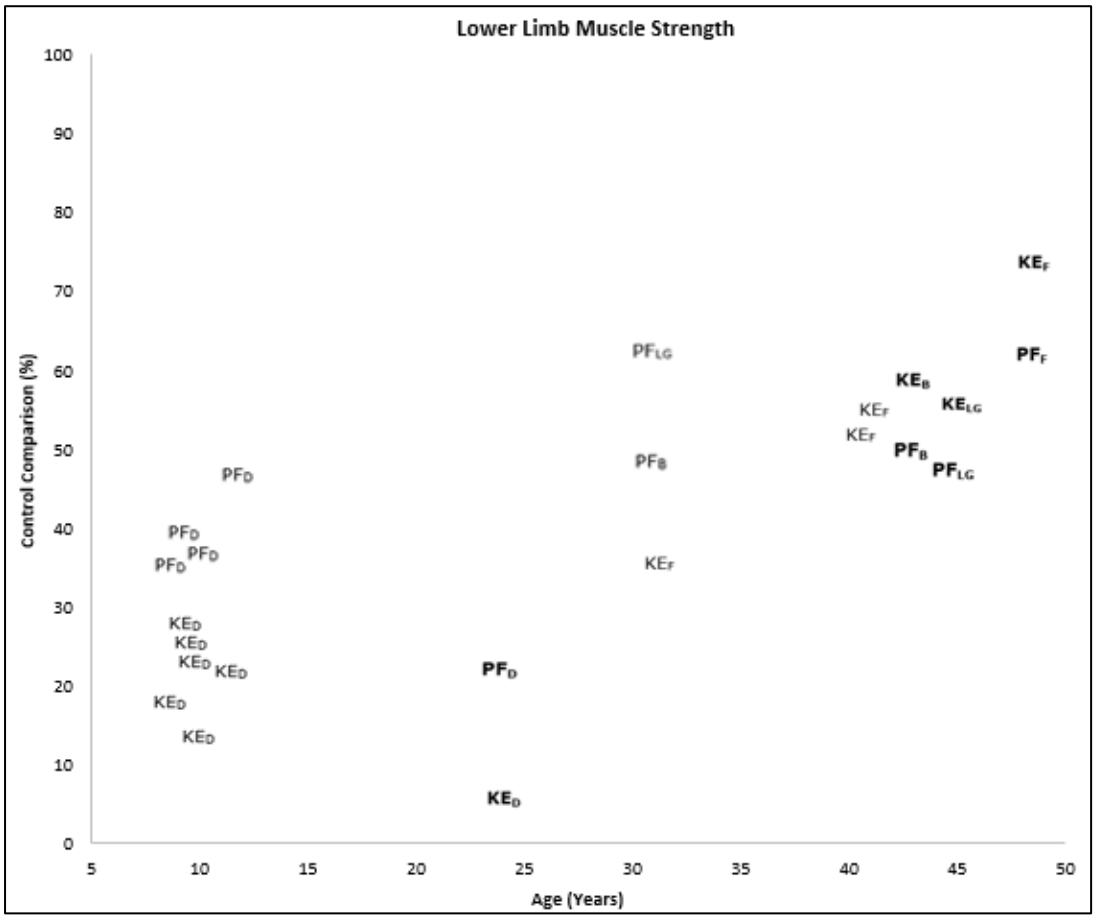


Figure 4.1. Muscle strength of PFMVC and KEMVC in DMD, BMD, LGMD and FSHD, based on comparisons relative to CTRL participants from Chapter 3 (Bold) and previous reports (Not Bold). Data is presented as the mean age of participants groups (X axis) to show the lifespan comparisons, and muscle strength as percentage of CTRL (Y axis). PF = Plantar-flexion maximal voluntary contraction; KE = Knee-extension maximal voluntary contraction $_{D}$ = Duchenne muscular dystrophy; $_{B}$ = Becker's muscular dystrophy; $_{LG}$ = Limb-Girdle muscular dystrophy; $_{F}$ = Facioscapulohumeral muscular dystrophy' CTRL = Control. (Bachasson et al., 2014; Forbes et al., 2013; Lott et al., 2014; Akima et al., 2012; Mathur et al., 2010; Skalsky et al., 2008; Skalsky et al., 2009; Wilson et al., 2018; Lerario et al., 2012; Løkken et al., 2016; Vohra et al., 2015; Wokke et al., 2014)

Previous PA data from dystrophic conditions has almost exclusively been presented from paediatric DMD populations (McDonald et al., 2005; Jeannet et al., 2011; Elliott et al., 2015). The only PA comparisons from adults with dystrophic conditions to CTRL have been presented in the form of self-reported PA history (Morse, 2016; Jacques et al., 2017). The use of quantitative measures of PA through tri-axial accelerometry allows for a much greater understanding of PA. Understandably, adults with DMD had the highest SB, however, the ability of some DMD participants to participate in forms of PA and the negative association between SB and LBM in the present chapter appears encouraging. Furthermore, these findings and recent work from Jansen et al. (2013), showing maintenance of function with the use or arm-cycle ergometers, suggests that PA should be encouraged through the use of adapted equipment and hydrotherapy.

The significant relationship between PA and KEMVC in BMD is a key finding from the current chapter. The relationships identified between TPA^{mins} and KEMVC in BMD is furthered by the stronger relationship of TPA^{mins} with 10m walk time in ambulant MD participants, and is consistent with those relationships identified within elderly populations (Foong et al., 2015; Santos et al., 2012) and paediatric DMD populations (Fowler et al., 2017). Furthermore, these findings add substantial value to current PA guidance in MD (Muscular Dystrophy Campaign, 2014). Future work is required to quantify activity thresholds relative to separate conditions, and between ambulant and non-ambulant individuals, in order to quantify PA intensities, and the relative intensities relationships with functional outcomes.

4.6 Conclusions

The present chapter quantifies lower limb muscle weakness (PFMVC and KEMVC) across four MD classifications, and can be used to add to the currently under-reported, yet clinically

observed, physiological understanding of conditions. Significant relationships were identified between muscle size and muscle strength of plantar-flexors in DMD adults. Furthermore, cross-sectional findings of PA in dystrophic conditions are presented, with significant increases in SB in all MD conditions compared to CTRL. Relationships have been identified between SB and reduced LBM, TPA^{Mins} and KEMVC in BMD, as well as TPA^{Mins} and 10m walk time in ambulant MD participants, suggesting PA should be encouraged, consistent with current MDUK guidelines. Future work however must quantify different PA intensities, as well as consider the safety and appropriateness of PA intensity relevant to MD classification. Chapter 5 will now focus on the self-perceived QoL in adults with MD, identifying the impact of muscle weakness on QoL, as well as a variety of previously identified variables (Chapter 2), such as pain and fatigue.

Chapter 5

Quality of Life in Adults with Muscular Dystrophy

This chapter is currently Under Review: Quality of Life in Adults with Muscular Dystrophy.

Quality of Life and Health Outcomes.

5.1 Abstract

Background

Muscle weakness is a defining characteristic of Muscular Dystrophy (MD); however, its impact on QoL in adults with MD remains unreported. This chapter aims to quantify QoL across four classifications of MD, and the impact of muscle weakness on QoL, as well as other previously identified determinants on QoL, such as pain and fatigue.

Methods

75 adults' males volunteered (15 DMD, 18 BMD, 12 LGMD, 14 FSHD and 15 CTRL). QoL measured by the SF36-v2 (8 domains); Knee Extension maximal voluntary contraction (KEMVC) measured by quantitative muscle testing; Fatigue measured by the Checklist Individual Strength Severity; Pain measured by a Visual Analog Scale (Pain VAS); ADLs measured by the Nottingham Extended Activities of Daily Living (NEADL); Self-Efficacy measured by The General Self-Efficacy Scale. Kruskal Wallis test was used to compare between groups, with post-hoc Mann-Whitney U pairwise comparisons used where appropriate. Stature was compared between groups using a one-way ANOVA, and Tukey's used for post-hoc comparison. Spearman's rank correlation analysis were used to identify associations between variables and domains of QoL

Results

QoL was lower across many domains in MD compared to CTRL. Within MD, FSHD scored lower than DMD for Role Physical, Vitality and Mental Health domains. KEMVC was only associated with Physical Function and Social Function domains for BMD. Pain, Self-Efficacy and ADLs associated with QoL domains in DMD, BMD and FSHD, with Fatigue the most consistently associated.

Conclusions

The present study has identified differences in QoL between MD classifications, especially within self-perceptions of mental health. The present study indicates that whilst muscle strength may be a defining feature of MD, it does not define self-perceived QoL in adults with MD. Comparatively, ADLs (DMD), Self-Efficacy and Pain (MD) were all associated with QoL domains, while Fatigue (MD) was the most consistent associate of QoL domains. Suggesting greater understanding of mental wellbeing and independence, and management of fatigue and pain are required to improve QoL for adults with MD.

5.2 Introduction

Irrespective of condition, all MDs typically present with muscle weakness (Chapter 4) and an eventual loss of ambulation, which are likely to reduce independence, and the self-perception of physical function (Gabriel and Bowling, 2004). The loss of muscle strength and function is commonly seen as a defining feature of MD and in Chapter 3 was associated with a) severity of the condition b) level of PA in ambulant adults, however its impact on perceived QoL remains unreported in adults with MD (McDonald et al., 2010). Therefore it is important to further understand the impact of declining muscle strength on QoL, but also in comparison to other variables such as pain and fatigue (Morís et al., 2017; Padua et al., 2009), that have previously been shown to impact QoL in MD.

QoL represents an individual's perception of their physical, mental and social functioning (Brazier et al., 1992), and is a meaningful measure of how a clinical condition may be impacting an individual. QoL has been reported previously in adults with MD, however, when multiple classifications of MD have been included within the same report classifications have been pooled (Grootenhuis et al., 2007; Ahlström and Gunnarsson, 1996; Abresch et al., 2002; Nätterlund and Ahlström, 2001). The variations in mutative-genetic cause (Emery, 2002), and clinical progression (Kilmer et al., 1995; C. M. McDonald et al., 1995; C. McDonald, R. Abresch, et al., 1995; C. McDonald, R. Johnson, et al., 1995), of each condition strongly suggest that each classification should be recognised and assessed independently, in order to detect possible differences in QoL between classifications of MD. In addition, greater understanding of the factors associated with QoL within different classifications of MD is required.

Given the progressive loss of strength and function associated with MD (Mathur et al., 2010), much research to date has focussed on the physical aspects of individual's lives, such as respiratory function (Kohler et al., 2005) and muscle strength (McDonald et al., 2010).

Associations between QoL and quantified muscle strength however remain unreported within adult populations with MD. By comparison, loss of muscle strength has previously been correlated with QoL in children with DMD (McDonald et al., 2010), and more broadly in MD a loss of muscle strength limits the ability to walk and perform functional tasks (Alfano et al., 2013), which are both facets contributing to QoL. In addition, increased BMI has been reported previously in adults with MD, and shown to impact not only function (Littleton, 2012), but also effect psychological well-being in CTRL (Taylor et al., 2013). Alternatively, psychological aspects such as self-efficacy (Bandura and Wood, 1989), an individual's confidence in their ability to overcome problems (Kohler et al., 2002), may provide a greater insight into QoL than physical impairment alone, and has been shown to be positively associated with QoL in other clinical conditions (Motl et al., 2009; Cunningham et al., 1991). Other perceived measures, including fatigue and pain, are also likely to impact upon QoL in all MD groups, and have indeed previously been shown to impact QoL in adults with DMD and FSHD (Morís et al., 2017; Padua et al., 2009; Pangalila, Van Den Bos, Bartels, Bergen, Stam, et al., 2015), but are not reported in adults with BMD or LGMD.

This study therefore, aimed to 1) compare the self-reported QoL of adults with DMD, BMD, LGMD and FSHD, and a non-MD CTRL group; 2) Present and compare between groups measures of Muscle Strength, Activities of Daily Living, Fatigue, Pain, Self-Efficacy and BMI 3) Identify associations between QoL domains and Muscle Strength, Activities of Daily Living, Fatigue, Pain, Self-Efficacy and BMI

This chapter hypothesises that measure of QoL will be lower in adults with MD compared to CTRL, while QoL will be comparable across MD conditions, except for the Physical Function

domain. KEMVC, Pain and CIS Severity will all be consistently associated with domains of QoL across MD.

5.3 Methods

Full details of methods can be found in Chapter 3, however in brief: this chapter consists of 75 adult males (15 DMD, 18 BMD, 12 LGMD, 14 FSHD and 15 CTRL). QoL measured by the SF36-v2 (8 domains); Body composition was assessed using BIA; KEMVC measured by quantitative muscle testing; Fatigue measured by the CIS Severity; Pain measured by the Pain VAS; ADLs measured by the NEADL; Self-Efficacy measured by The General Self-Efficacy Scale..

5.3.1 Statistical Analysis

All analysis was performed using IBM SPSS Statistics v21 software. The critical level of statistical significance was set at 5%. All data is presented as mean ±SD, unless stated otherwise in the table legend. Tests for parametricity (Shapiro-Wilks and Levenes) were performed upon participants' anthropometrics and KEMVC, with all questionnaire data interpreted as non-parametric. All data, except for stature was parametric. Kruskal Wallis test was used to compare between groups, with post-hoc Mann-Whitney U pairwise comparisons used where appropriate. Stature was compared between groups using a one-way ANOVA, and Tukey's used for post-hoc comparison. Spearman's rank correlation analysis were used to identify associations between variables and domains of QoL with ±0.30-0.49 considered weak, ±0.50-0.69 considered moderate and ±0.70+ considered strong (Mukaka, 2012).

Note: Due to the high volume of variables in this chapter, differences are reported in respective sections and statistical significance reported in respective tables.

5.4 Results

5.4.1 Participant Characteristics

Data detailing participant characteristics is summarised in Table 5.1. DMD were younger than all other groups, and FSHD were older than CTRL. No differences were found between groups for stature. DMD were lighter than other MD groups, and LGMD were heavier than CTRL. No differences were found between groups for BMI.

Table 5.1 Participant Characteristics and Anthropometrics

	DMD	BMD	LGMD	FSHD	CTRL
n	15	18	12	14	16
Age (Years)	24.2 ±6.1 B***,LG***,F***,C*	42.4 ±13.5	41.6 ±11.7	47.1 ±11.1 C*	35.4 ±12.7
Stature (cm)	172.0 ±4.3	177.4 ±6.0	179.6 ±7.2	178.6 ±8.1	177.5 ±9.3
Mass (Kg)	73.1 ±14.6 B*,LG**,F*	86.5 ±20.3	97.0 ±18.1 C*	86.0 ±11.2	81.1 ±18.2
Ambulant	0/15	10/18	3/12	10/14	16/16
BMI (kg/m^2)	25.5 ±4.1	27.3 ±6.2	29.4 ±26.6	26.6 ±3.4	25.5 ±3.7

Table 5.1. Participant's anthropometric characteristics. DMD = Duchenne Muscular Dystrophy; BMD = Beckers Muscular Dystrophy; LGMD = Limb-Girdle Muscular Dystrophy; FSHD = Facioscapulohumeral Muscular Dystrophy; cm = centimetres; Kg = Kilograms; BMI = Body Mass Index; ^{B} denotes significant difference from BMD; ^{LG} denotes significant difference from LGMD; ^{F} denotes significant difference from FSHD; ^{C} denotes significant difference from CTRL; * denotes P<.05; ** denotes P<.01; *** denotes P<.001.

5.4.2 Quality of life

Data detailing QoL in the study sample is summarised in Table 5.2. For consistency across domains, higher scores are indicative of higher QoL, e.g. Bodily Pain domain was higher in CTRL than all MD i.e. all MD reported more pain, therefore scoring lower.

The Physical Function and Role Physical domains were lower in all MD groups compared to CTRL. Within MD, the Physical Function domain was lower in DMD than BMD and FSHD. The

Role Physical domain was higher in DMD than FSHD. The Vitality domain was lower in BMD and FSHD compared to CTRL. In addition, DMD reported a higher Vitality domain than FSHD. No other differences were found between groups for Vitality.

Within the Role Emotional domain, DMD, BMD and FSHD were lower than CTRL. The Role Emotional domain, was higher in LGMD than FSHD. No other differences were found between groups for the Role Emotional domain.

The Bodily Pain, Social function and General Health domains were lower in all MDs compared to CTRL, with no differences found between MD groups. The Total Physical domain was lower in all MDs compared to CTRL. No other differences were found between groups for the Total Physical domain. No differences were found between groups for Total Mental domain. Total SF6D domain was lower in all MDs compared to CTRL. No other differences were found between groups for Total SF6D domain.

Table 5.2 SF-36v2 in MD

	DMD	BMD	LGMD	FSHD	CTRL
Physical Function	1.3 ±3.5 B**,F**,C***	18.4 ±18.2 C***	6.3 ±10.3C***	18.2 ±12.5 C***	95.9 ±9.3
Role Physical	72.1 ±26.1 F*,C**	53.8 ± 32.5 C***	59.9 ±31.5 C***	41.5 ±26.7 C***	99.2 ±2.1
Bodily Pain	66.1 ±16.4C*	58.6 ±22.2C**	56.1 ±24.4C**	48.1 ±28.6C***	87.1 ±15.8
General Health	55.6 ±20.1 C**	48.4 ±19.3 C***	43.3± 22.5 C***	44.1 ±24.2 C***	81.7 ±11.2
Vitality	63.3 ±18.0F***	50.0 ±24.7C*	51.6 ±17.3	37.9 ±16.9C***	72.3 ±19.2
Social Function	84.1 ±41.9C*	68.8 ±30.4 C**	76.0 ±27.4 C*	67.9 ±29.7 C**	97.7 ±6.8
Role Emotional	80.6 ±24.5C*	66.2 ±32.6 C**	86.8 ±25.7 F*	69.0 ±24.1 C**	98.4 ±4.5
Mental Health	79.0 ±14.9 F*	74.2 ±16.0 C*	78.8 ±14.6	65.0 ±19.1C**	84.7 ±8.5
Total Physical Score	34.3 ±5.4 C***	34.5 ±6.7 C***	30.2 ±5.8 C***	30.8 ±6.3 C***	56.8 ±3.6
Total Mental Score	58.2 ±10.5	51.8 ±9.3	58.3 ±9.7	49.8 ±11.0	55.8 ±3.6
Total SF6D	.646 ±0.109 C***	.643 ±0.118 C***	.611 ±0.071 C***	.589 ±0.122 C***	.896 ±0.101

Table 5.2 SF36-v2 outcomes. Presented as mean ± SD. DMD = Duchenne Muscular Dystrophy; BMD = Becker's Muscular Dystrophy; LGMD = Limb-Girdle Muscular Dystrophy; FSHD = Facioscapulohumeral Muscular Dystrophy; ^{B} denotes significant difference from BMD; ^{LG} denotes significant difference from LGMD; ^{F} denotes significant difference from FSHD; ^{C} denotes significant difference from CTRL; * denotes significance <0.05; ** denotes significance <0.01; *** denotes significance <0.001.

5.4.3 Strength

The associations between QoL and impairment are detailed in Table 5.3. KEMVC was less in DMD, BMD, LGMD groups compared to CTRL. Similarly, DMD were weaker than BMD, LGMD and FSHD groups, respectively. No other KEMVC differences were found between groups. No other differences were found between groups.

5.4.4 Questionnaires

The associations between QoL and perceptions are also detailed in Table 5.3. Thus, the reported severity of CIS Severity was higher in all MD groups compared to CTRL participants. Furthermore, FSHD participants scored higher on CIS Severity than DMD and BMD groups, respectively. No other differences were found between groups for CIS Severity. DMD participants reported lower than all other groups on the NEADL scale. No other differences were found between groups. Furthermore, CTRL participants scored higher than BMD, LGMD and FSHD, respectively. All MD groups reported higher levels of pain compared to CTRL participants. There were no differences in pain between MD groups. There were no differences between any groups for the General Self-Efficacy Scale.

Table 5.3 Measures of Impairment and Perception

	DMD	BMD	LGMD	FSHD	CTRL
CIS Severity	34.4 ±8.7 ^{F*,C***}	33.2 ±10.5 ^{F**,C***}	34.4 ±10.9 ^{C***}	43.0 ±5.3 ^{C***}	14.1 ±6.1
VAS Pain	2.5 ±1.6 ^{C**}	3.5 ±2.5 ^{C***}	3.6 ±2.8 ^{C***}	3.9 ±2.2 ^{C***}	0.4 ±0.7
KEMVC (N.m)	12.6 ±8.8 ^{B***,} ^{LG***,F***,C***}	96.6 ±60.0 ^{C**}	98.2 ±56.4 ^{C*}	123.6 ±78.2	164.6 ±55.9
NEADL	13.9 ±6.0 ^{B***,LG*,F***,C***}	36.7 ±14.4^{C***}	29.3 ±7.1 ^{C***}	39.4 ±14.6^{C**}	63.6 ±3.1
General Self-Efficacy	31.0 ±6.2	28.3 ±5.9	31.0 ±5.1	30.7 ±7.5	34.3 ±4.3

Table 5.3 Measures of Impairment and Perception. DMD = Duchenne Muscular Dystrophy; BMD = Beckers Muscular Dystrophy; LGMD = Limb-Girdle Muscular Dystrophy; FSHD = Facioscapulohumeral Muscular Dystrophy; CIS = Checklist Individual Strength; VAS = Visual Analog Scale; KEMVC = Knee Extension Maximal Voluntary Contraction; N.m = Newton Metres; NEADL = Nottingham Extended Activities of Daily Living; ^{B} denotes significant difference from BMD; ^{LG} denotes significant difference from LGMD; ^{F} denotes significant difference from FSHD; ^{C} denotes significant difference from CTRL; * denotes significance P<0.05; ** denotes significance P<0.01; *** denotes P<0.001.

5.4.5 QoL Correlations

The following brief description of associations (or lack therefore of), are summarised in Table 5.4 below.

5.4.5.1 BMI

The Social Function domain was moderately associated with BMI, while the Vitality domain, Total Mental Score and SF6D were all strongly associated with BMI, in LGMD. No other associations were identified with BMI.

5.4.5.2 Strength

The Physical Function and Social Function domains were also moderately associated with KEMVC in BMD. No other associations were identified with strength.

5.4.5.3 Perception

Physical Function domain was associated with NEADL, moderately in DMD and BMD, and strongly in FSHD. The Role Physical domain was strongly associated with CIS Severity in DMD and FSHD. In addition, Role Physical domain was also moderately associated with Self-Efficacy in DMD. The Bodily Pain domain was associated with the VAS Pain scale in BMD (strong) and FSHD (moderate).

The General Health domain was moderately associated with CIS Severity in DMD, BMD and LGMD, and VAS Pain in BMD. The Vitality, Bodily Pain and General Health domains were moderately associated with NEADL in DMD.

The Vitality domain was moderately associated with CIS Severity in DMD. BMD moderately associated both CIS Severity and VAS Pain with the Vitality domain. While both Vitality and Social Function domains were moderately associated with CIS Severity in FSHD.

The Role Emotional domain was moderately associated with Self-Efficacy in DMD and BMD, respectively. In addition, Role Emotional domain was associated with CIS Severity in DMD

(moderate) and FSHD (strong). The Mental Health domain was moderately associated with CIS Severity in both BMD and FSHD.

Total Physical Score was moderately associated with CIS Severity in BMD, while VAS Pain was associated with Total Physical Score in both BMD (weak) and FSHD (moderate). Total Mental Score showed strong associations with CIS Severity in FSHD.

SF6D was associated with CIS Severity in DMD (moderate) and FSHD (strong), respectively.

Table 5.4 Associations of SF-36v2 domains.

SF-36v2	BMI	KEMVC	NEADL	CIS Severity	VAS Pain	Self-Efficacy
Physical Function	-	0.609^{B**}	0.595^{D*} 0.654^{B**} 0.751^{F**}	-	-	-
Role Physical	-	-	-	-0.769 ^{D**} -0.759^{F**}	-	0.534^{D*}
Bodily Pain	-	-	0.613^{D*}	-	-0.715^{B**} -0.694^{F**}	-
General Health	-	-	0.564^{D*}	-0.525^{D*} -0.620^{B**} -0.644^{LG*}	-0.602^{B**}	-
Vitality	- 0.800^{LG**}	-	0.533^{D*}	-0.548^{D*} -0.533^{B*} -0.668^{F**}	-0.558^{B*}	0.590^{D*} 0.541^{F*}
Social Function	-0.643^{LG*}	0.544^{B*}	-	-0.594^{F*}	-	-
Role Emotional	-	-	-	-0.544^{D*} -0.851^{F***}	-	0.570^{D*} 0.600^{B**}
Mental Health	-	-	-	-0.588^{B*} -0.575^{F*}	-	-
Total Physical Score	-	-	-	-0.597^{B**}	-0.476^{B*} -0.683^{F**}	-
Total Mental Score	- 0.748^{LG**}	-	-	-0.884^{F**}	-	-
SF6D	- 0.720^{LG**}	-	-	-0.569^{D*} -0.884^{F**}	-	-

Table 5.4 Associations of SF-36v2 domains. BMI = Body Mass Index; KEMVC = Knee Extension Maximal Voluntary Contraction; NEADL = Nottingham Extended Activities of Daily Living; CIS = Checklist Individual Strength; VAS = Visual Analog Scale; ^{D} denotes significant association in DMD; ^{B} denotes significant association in BMD; ^{LG} denotes significant association in LGMD; ^{F} denotes significant association in FSHD; - denotes no significant associations; * denotes association of <0.05; ** denotes association of <0.01; *** denotes association of <0.001.

5.5 Discussion

The present study assesses QoL across four separate classifications of adults with MD, as well as presenting a range of factors that are associated with QoL. The findings show that adults

with MD typically scored poorer QoL when compared with CTRL. Furthermore, the QoL of adults with different classifications of MD were largely comparable with the exception of the Physical Function domain, and domains associated with mental wellbeing. Furthermore, the findings from this study highlight that despite progressive muscle weakness being a clinical feature of MD, it is not consistently associated with QoL in adults with MD; specifically, KEMVC was associated with 2/11 domains in BMD only. By contrast, QoL domains were more frequently associated with ADLs (4/11 in DMD), pain (4/11 in BMD, 2/11 in FSHD), and self-efficacy (4/11 in DMD, 1/11 in BMD and FSHD). Fatigue was the most consistent associate of QoL in adults with DMD (5/11 domains), BMD (4/11), LGMD (1/11) and FSHD (7/11 domains). In addition, higher BMI appeared a consistent negative associate of QoL in adults with LGMD (4/11).

The poorer QoL observed in adults with MD is consistent with other reports of MD and in other conditions where physical function is impaired (Picavet and Hoeymans, 2004; Abresch et al., 2002; Ahlström and Gunnarsson, 1996; Grootenhuis et al., 2007). In the present study however, differences between the QoL of adults with different classifications of MD, in domains other than physical function were identified. Unsurprisingly, differences in Physical Function appeared consistent with the clinical progression of each individual condition (Emery, 2002), and the severity of weakness described in Chapter 3. As would be expected given the severity of the condition, DMD scored lowest for physical function (Bendixen et al., 2014; Mathur et al., 2010). Despite the lower Physical Function score, adults with DMD scored higher than adults with FSHD across Vitality, Role Physical and Mental Health domains. It is possible that this could be attributed to better coping mechanisms within DMD, as has been suggested previously in adolescents with DMD (Uzark et al., 2012). Adults with FSHD may be less likely to have these coping mechanisms, possibly due to the later onset of the condition

(Padberg, 1982), leading to large changes in individual's lives and possible comparisons to an individual's pre-condition state. By comparison, DMD is a life-long condition (C. McDonald, R. Abresch, et al., 1995), therefore acceptance of the condition and limitations may be easier or occur earlier. Nonetheless, these assumptions are speculative and require greater investigation beyond the scope of this thesis, which identified impaired strength and ROM as clinical features of MD and therefore primary outcome measures (Chapters 1 and 2). Interestingly though, adults with FSHD also scored lower than adults with LGMD for Role Emotional and Mental Health domains, despite both conditions having a characteristically later onset (Huml, 2015).

Within adults with MD, the level of physical impairment is typically seen as the defining characteristic of the condition (McDonald et al., 2013), and was therefore theorised as a key associate of QoL. Within the present study however, KEMVC was only associated with Physical Function and Social Function domains in adults with BMD. Similarly, previous research has shown no association between the Physical Function domain and respiratory function in adults with DMD (Kohler et al., 2005), however within ambulant children with DMD, KEMVC was shown as a good predictor of QoL determined Physical Function (McDonald et al., 2010). The Physical Function domain showed more consistent associations with ADL across conditions, which can be interpreted in two ways; firstly, that an individual's level of independence, rather than just function, influences QoL; or, secondly, that the physical function assessment of the SF-36v2 is an assessment of physical independence, rather than function. This is further evidenced by the reflection of the Physical Function scores upon ambulatory status, suggesting the Physical Function domain of the SF-36v2 may be less appropriate for non-ambulant individuals (Haran et al., 2007). For example, all SF36-v2 questions regarding physical function relate to walking (Appendix 4), which is limited within

the population and as evidenced in Chapter 4, significant differences can still be found between lower limb function between different populations that are both largely non-ambulant (DMD vs BMD and LGMD). In comparison the NEADL does include so questions related to walking (Appendix 5), however also includes broader independent questions, such as those regarding controlling money and emails. Therefore, the results from the present chapter suggests further development and validation of the SF-36 walk-wheel (Lee et al., 2009) may be required. The Walk-Wheel has further adapted the SF36-v2 by adding 3 further questions related to physical function, whereby questions 8-10 of the SF36-v2 are repeated, however the word "Walked" is replaced with the word "Wheeled" (Appendix 9). Furthermore, the use of a single strength measure of KEMVC, previously identified as relevant to ADLs of high intensity, are beyond the capacity of many adults with MD (Skelton and McLaughlin, 1996). KEMVC may not be as relevant to QoL in adults with MD particularly those who are non-ambulatory. The associations of NEADL with QoL, especially in adults with DMD, signifies independence, ownership and being able to undertake broader aspects of daily life (potentially using adaptive measures), rather than lower limb function (i.e. KEMVC), has a positive influence on QoL in DMD. The provision of support to empower adults with DMD to be able to undertake daily tasks should therefore be considered essential for the maintenance of their QoL.

Pain and fatigue levels are higher in MD groups than CTRL within the present study, consistent with those that have previously identified pain and fatigue in adults with FSHD and DMD (Abresch et al., 2002; Padua et al., 2009; Pangalila, Van Den Bos, Bartels, Bergen, Stam, et al., 2015). The elevated pain and fatigue levels in BMD and LGMD adults are however, comparable to DMD and FSHD adults, suggesting that fatigue and pain may be symptomatic of MD, rather than specific conditions (Bushby et al., 1998). In addition, the elevated fatigue

of adults with FSHD in comparison to other MD groups, as well as CTRL, identifies a condition specific need for further investigation and condition specific interventions (Kalkman et al., 2005). Furthermore, the consistent associations of fatigue and pain across the MD conditions with aspects of QoL highlights their impact on both physical and mental well-being (Kalkman et al., 2005). Similar associations between pain and fatigue have been identified in other clinical conditions (Rupp et al., 2004; Motl et al., 2009), as well as in adults with DMD and FSHD (Morís et al., 2017; Pangalila, Van Den Bos, Bartels, Bergen, Stam, et al., 2015). This finding suggests that there is the potential for interventions that are known to reduce pain and fatigue in other clinical conditions, such as acupuncture (Vickers et al., 2012), physiotherapy (Jansen et al., 2011; Smart et al., 2016), and where possible, PA (as has been applied in FSHD (Voet et al., 2014)), may be applicable in adults with MD and could possibly improve QoL.

No differences between any of the present MD conditions and CTRL were observed for self-efficacy, which would appear as a positive outcome, with physical manifestations of MD not influencing an individual's confidence to overcome problems. Interestingly however, self-efficacy was positively associated with QoL domains, particularly within the DMD group. The authors propose this could be attributed to the severe loss of physical function associated with DMD (Mathur et al., 2010), subsequently individuals may develop higher problem solving and coping capabilities, resulting in the higher Role Physical, Role Emotional and Vitality domains evidenced in the current study. Further interventions in the treatment strategy of those with DMD, and more broadly all of the MDs, should address the psychosocial issues identified in the present study, as they suggest possible improvements in the QoL of adults with MD.

Despite the wide variance in the physical manifestation of these MD conditions, as demonstrated in Chapter 3, the present chapter displays all adults with MD to have lower QoL compared to CTRL, with some specific differences between MD classifications in individual domains of QoL. The largest differences in QoL between MD classifications were between the Physical Function domain, consistent with the classical definitions of these conditions (Emery, 2002), other differences were identified however, between classifications across domains associated with mental and psychological wellbeing. This finding suggests that classing these forms of MD together when examining QoL (Ahlström and Gunnarsson, 1996; Nätterlund and Ahlström, 2001), as seen previously, is not appropriate given the specific differences identified. Independently, a range of variables were associated with QoL domains, with the most frequent associations being found with activities of daily living, self-efficacy and pain; it was however, fatigue that was most consistently associated with multiple QoL domains, across all MD conditions.

5.6 Conclusion

Differences identified in domains of QoL in the present chapter suggests a greater focus is required, and further investigation is needed into mental health and wellbeing, particularly in conditions such as FSHD. It is proposed that later onset of this condition may have a large impact on psychosocial aspects associated with QoL. Furthermore, ADLs were only associated with QoL domains, other than Physical Function, in adults with DMD, highlighting the importance of independence in this condition. In addition, consistent associations of pain and fatigue across QoL domains, across MD classifications, indicates a need for future investigation into the management and treatment of pain and fatigue within adults with MD. While this chapter had identified QoL, coping mechanisms and measures of subjectivity as important, the description of physiological impairments in adults with MD remains lacking, as

identified in Chapter 2, therefore further understanding of the physical impairments associated with clinical features of MD is still required. Impaired RoM and its neuromuscular determinants will therefore be assessed in Chapter 6.

Chapter 6

Neuromuscular Determinants of Range of Motion in Adults with Muscular Dystrophy

6.1 Abstract

Background

Limited passive ankle range of motion ($ROM^{Passive}$) is commonly recognised in muscular dystrophy (MD), especially children with Duchenne MD (DMD), however the limitation of active ROM (ROM^{Active}) remains to be reported. Similarly, the morphological and stiffness properties associated with ankle ROM that could limit ROM in adults with MD, are unreported.

Methods

This chapter included 72 participants including: 16 non-MD control (CTRL), 15 DMD, 17 Beckers (BMD), 13 Limb- Girdle (LGMD), 16 Facioscapulohumeral (FSHD). Body fat (%) and lean body mass (LBM) were measured using bioelectrical-impedance. Ankle plantarflexion (PF)-dorsiflexion (DF) $ROM^{Passive}$ and ROM^{Active} were measured using electro—goniometry. Muscle morphology, including displacement of the muscle-tendinous junction (MTJ) through $ROM^{Passive}$, of the Gastrocnemius Medialis (GM) were determined by B-mode ultrasound. GM stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the distal displacement of the MTJ. Muscle-tendon unit (MTU) stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the ankle angle. Isometric maximal voluntary contraction (MVC) was assessed during plantar-flexion (PFMVC) using a load cell. The Kruskal Wallis test was used to compare between groups, with post-hoc Mann-Whitney U pairwise comparisons where appropriate. Parametric data was compared using a one-way ANOVA, and Tukey's for post-hoc comparison. Kendall Tau correlations were used to identify associations of non-parametric data and Pearson's correlation coefficient of parametric data, between age, L^{GM}, strength and stiffness properties with $ROM^{Passive\ and}$ ROM^{Active} measures

Results

CTRL participants had 82%, 55%, 60% and 56% greater ROM^{Active} than DMD, BMD, LGMD and FSHD, respectively. $ROM^{Passive}$ was 66%, 34%, 44% and 35% greater in CTRL compared to DMD, BMD, LGMD and FSHD, respectively. DMD had smaller ROM^{Active} and $ROM^{Passive}$ than BMD (60%, 49%), LGMD (54%, 39%) and FSHD (58%, 48%). GM stiffness was 29%, 46%, 40% and 55% higher in DMD than BMD, LGMD, FSHD and CTRL, respectively. In all MD, PFMVC was associated with ROM^{Active} (r= 0.376-0.750). $ROM^{Passive}$ was associated with passive properties of MTU Stiffness (r= -0.464) and GM Stiffness (r= -0.391) in DMD and BMD, respectively.

Conclusions

In conclusion, the present chapter has quantified limited ankle DF/PF ROM in four classifications of adults with MD, identifying muscle weakness and increased stiffness as associations of ankle ROM.

6.2 Introduction

While progressive muscle weakness is the most common characteristic of MD, and the focus of Chapters 4 and 5, ROM of joints has similarly long been recognised as limited with the progression of MD (Johnson et al., 1992). Particular focus has been given to the sagittal plane ROM of the ankle (Halar and Bell, 1988; Archibald and Vignos Jr, 1959), which is the focus of this chapter and unless otherwise stated, ROM is referring to the sagittal plane of the ankle. Limited ROM of the ankle has been described as a characteristic of DMD (Bushby et al., 2010). In milder forms of MD, such as those discussed in Chapter 1, limited ROM has also been reported, particularly following the loss of ambulation (Kilmer et al., 1995; C. M. McDonald et al., 1995; C. McDonald, R. Johnson, et al., 1995).

The $ROM^{Passive}$ has been reported as limited in 78% of children with DMD (n=46, 14 years) and 57%, 25% and 42% of adults with BMD (n=7, 21 years), LGMD (n= 12, 45 years) and FSHD (n=40, 49 years), respectively (Johnson et al., 1992). In addition, $ROM^{Passive}$ loss, in children with DMD, and adults with BMD, LGMD and FSHD, at the ankle was reported as between 15-44° (where normal ROM would be ~60deg PF to DF) (Johnson et al., 1992). Limitations of $ROM^{Passive}$ will restrict the ROM^{Active} in MD, however ROM^{Active} in adults with MD, and $ROM^{Passive}$ in adults with DMD, have yet to be quantified, and more broadly, mechanisms of limited $ROM^{Passive}$ across MD remain to be quantified.

A reduction in ankle $ROM^{Passive}$ within MD has previously been attributed to fibrotic changes to the muscle, reduced muscle strength (limiting the ability to actively maintain ROM), and static positioning of the ankle in PF resulting in equinus deformity (Dubowitz, 1964; Brooke et al., 1989; Hsu and Furumasu, 1993). There is however little, if any, experimental evidence describing the possible factors limiting ROM in adults with MD. Furthermore, current reports of ROM are restricted to $ROM^{Passive}$ (Archibald and Vignos Jr, 1959; Johnson et al., 1992), which

although representing the impairments to the passive flexibility of a joint, may not fully reflect functional impairments (Ross and Engsberg, 2007). In contrast, the ankle ROM achieved by an individual, independently, through ROM^{Active}, reflects the ability to perform functional tasks and could be indicative of fall risk, as was identified in the elderly (Menz et al., 2006; Menz et al., 2005).

Stiffness of the MTU can be assessed through the passive torque-angle relation of the muscle-tendon joint under stretch and contributes to the $ROM^{Passive}$ (Sale et al., 1982; Nakamura, 2011). Whereas the individual muscle stiffness can be assessed by tracking the distal displacement of the GM MTJ using ultrasonography whilst the MTU is stretched, hereafter referred to as GM stiffness (Morse, 2011; Morse et al., 2008). Increased GM stiffness in children with DMD has previously been determined through supersonic shear imaging at two muscle lengths, "shortened" and "stretched" (Lacourpaille et al., 2015). MTU and GM stiffness throughout the ROM in adults with DMD or other forms of MD remain unreported. Furthermore, no associations have been made between morphological characteristics of the muscle, MTU stiffness or GM stiffness, and $ROM^{Passive}$.

Although the MTU and GM stiffness are unreported in adults with MD, a potential mechanism by which ROM could also be limited in MD is through reductions in GM length (L^{GM}) as has been described in adults with DMD and BMD (Jacques et al., 2017; Morse et al., 2015). Shortened L^{GM}, possibly attributed to the atrophic processes of the condition and the static-positioning/immobility when in a seated position, is likely to reduce ankle ROM by limiting length-tension properties of the GM (Spector et al., 1982), and by predisposing the joint to ankle equinus (Williams et al., 1984). To date however, no study has reported associations

between the stiffness, strength and muscle length properties identified, and ROM in adults with MD.

The aim of the present chapter was to 1) compere ROM^{Active} and $ROM^{Passive}$ in adults with MD and CTRL. 2) Compare levels of MTU and GM stiffness in adults with MD and CTRL. 3) Identify associations of ROM with measures of muscle weakness, stiffness and muscle length.

This chapter hypothesises that measures of ROM^{Active} and $ROM^{Passive}$ will be lower, while MTU stiffness and GM stiffness measures will both be increased, in MD groups compared to CTRL. MTU stiffness and GM stiffness will be associated with measures of $ROM^{Passive}$ and muscle weakness will be associated with measures of ROM^{Active}.

6.3. Methods

Full details of methods can be found in Chapter 3, however in brief: this chapter included 72 participants including: 16 CTRL, 15 DMD, 17 BMD, 13 LGMD, 16 FSHD. Body fat (%) and LBM were measured using bioelectrical-impedance. Ankle; PF, DF, $ROM^{Passive}$ and ROM^{Active} were measured using electro—goniometry. Muscle morphology, including displacement of the GM MTJ through $ROM^{Passive}$, were determined by B-mode ultrasound. GM stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the distal displacement of the MTJ. MTU stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the ankle angle. PFMVC was assessed using a load cell..

6.3.1 Statistical Analysis

IBM Statistics 21 software was used to perform all analyses with a critical level of statistical significance set at 5%. Tests for parametricity (Shapiro-Wilks and Levenes) were performed upon all variables. All data, except for height, L^{Tibia}, L^{GM} and $ROM^{Passive}$, were non-parametric. The Kruskal Wallis test was used to compare between groups, with post-hoc Mann-Whitney

U pairwise comparisons where appropriate. Parametric data was compared using a one-way ANOVA, and Tukey's for post-hoc comparison. Due to significant differences in L^{Tibia}, measures of L^{GM}, L^{Tendon} and L^{MTU}, ANCOVAs were performed to determine whether differences remained when L^{Tibia} was controlled for. Kendall Tau correlations were used to identify associations of non-parametric data and Pearson's correlation coefficient of parametric data, between age, L^{GM}, strength and stiffness properties with $ROM^{Passive\ and}$ ROM^{Active} measures. Correlations of ±.30-.49 are considered weak, ±.50-.69 considered moderate and ±.70+ considered strong. Where relevant, comparisons are presented with P values and the relative difference (%) from a named experimental group. When values are both positive and negative, only P values have been presented.

6.4 Results

6.4.1 Anthropometrics, Body Composition and MTU Morphology

DMD participants were younger than those with BMD (44%, P<0.001), LGMD (37%, P=0.003), FSHD (49%, P<0.001) and CTRL (33%, P=0.006). FSHD were also older than CTRL participants (24%, P=0.032). LGMD participants were heavier than both DMD (22%, P=0.002) and CTRL (P=0.017) groups. DMD participants had lower LBM than BMD (19%, P=0.002), LGMD (23%, P=0.001), FSHD (19%, P=0.011) and CTRL (26%, P<0.001). No other differences were identified between groups for any other anthropometric or body composition measures (P>0.05, Table 6.1).

DMD participants had shorter L^{Tibia} than BMD (15%, P<0.001), LGMD (14%, P<0.001), FSHD (15%, P<0.001) and CTRL (18%, P<0.001) participants. Initial differences were identified for L^{GM} with DMD shorter than all other groups (P<0.05), however when L^{Tibia} was controlled for in an ANCOVA no differences were identified between any groups for L^{GM} (P>0.05). DMD participants had shorter L^{Tendon} than BMD (17%, P=0.001), LGMD (17%, P=0.014), FSHD (18%,

P=0.001) and CTRL (23%, P<0.001) participants. All differences remained when L^{Tibia} was controlled for in an ANCOVA (P<0.05). L^{MTU} was shorter in DMD participants than BMD (17%, P<0.001), LGMD (16%, P=0.002), FSHD (18%, P<0.001) and CTRL (22%, P<0.001) participants. In addition, BMD participants (7%, P=0.028) had a shorter L^{MTU} than CTRL. All significances remained when L^{Tibia} was controlled for in an ANCOVA (P<0.05), in addition LGMD was shown to have a shorter L^{MTU} than CTRL (8%, P=0.045). CTRL had a bigger L^{GM}/L^{MTU} ratio than DMD (P=0.021). No other differences were identified between groups for L^{Tibia}, L^{GM}, L^{Tendon}, L^{MTU} or L^{GM}/L^{MTU} (P>0.05, Table 6.1).

Table 6.1. Participant Characteristics, Care and Muscle Morphology

	DMD	BMD	LGMD	FSHD	CTRL
N	16	17	10	13	16
Age (Years)	23.8 (6.1) ^{B,LG,F,C}	42.5 (14.0)	37.9 (8.4)	46.3 (11.2)^{C}	35.4 (12.7)
Height (cm)	172.2 (4.2)	177.5 (6.1)	178.7 (7.6)	178.9 (8.4)	177.5 (9.3)
Mass (Kg)	75.9 (18.1)^{LG}	87.2 (18.3)	97.3 (18.0)^{C}	84.19 (9.4)	81.11 (18.2)
LBM (Kg)	49.1 (9.5) ^{B,LG,F,C}	60.3 (7.2)	63.6 (10.3)	60.2 (8.4)	66.0 (13.2)
Ambulant	0/16	8/17	3/10	10/13	16/16
Physiotherapy Monthly Frequency (Range)	4 (1-4)	2 (1-2)	2 (1-2)	2 (1-2)	0 (-)
Orthotics	5/16	0/17	0/10	4/13	0/16
L^{Tibia} (cm)	33.1 (2.5)^{B,LG,F,C}	38.8 (2.5)	38.6 (2.9)	38.8 (2.1)	40.4 (4.4)
L^{GM} (cm)	17.3 (1.9) ^{B,LG,F,C}	21.4 (3.1)	21.5 (2.9)	21.9 (2.5)	23.2 (3.1)
L^{Tendon} (cm)	17.1 (2.0) ^{B,LG,F,C}	20.1 (2.0)	19.7 (2.2)	20.2 (1.7)	21.4 (3.0)
L^{MTU} (cm)	34.6 (2.9) ^{B,LG,F,C}	41.5 (3.2)^{C}	41.2 (4.0)^{C}	42.1 (2.3)	44.5 (4.0)
L^{GM}/L^{MTU} (%)	50.3 (3.9)^{C}	51.4 (5.0)	52.2 (4.2)	51.9 (4.1)	53.0 (5.4)

Table 6.1. Participant Characteristics and Body Composition. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD – Facioscapulohumeral Muscular Dystrophy, LBM = Lean Body Mass, cm = centimetres, Kg = Kilograms, L^{Tibia} = Tibia Length, L^{GM} = Gastrocnemius Medialis Length, L^{MTU} = Muscle Tendon Unit Length. ^{B} denotes significant difference from BMD, ^{LG} denotes significant difference from LGMD, ^{F} denotes significant difference from FSHD, ^{C} denotes significant difference from CTRL.

6.4.2 Range of Motion

DMD participants resting angle was more plantar-flexed than BMD (43%, P=0.002), LGMD (36%, P=0.013), FSHD (46%, P=0.001) and CTRL (44%, P=0.002) groups. There were no other differences between groups for resting angle (P>0.05, Table 6.2).

Max PF^{Active} was and in greater PF in DMD than BMD (P=0.048) and FSHD (P=0.015) groups. CTRL participants Max PF^{Active} was in greater PF than BMD (P=0.003), LGMD (P=0.034) and FSHD (P=0.001) groups. Max DF^{Active} was lower in DMD participants than BMD (P<0.001), LGMD (P=0.037), FSHD (P=0.001) and CTRL (P<0.001) participants. CTRL participants had greater Max DF^{Active} than BMD (P<0.001), LGMD (P<0.001) and FSHD (P=0.001) groups. No other differences were found between groups for Max PF^{Active} or Max DF^{Active} (P>0.05, Table 6.2).

No differences were found between groups for Max $PF^{Passive}$ (P>0.05). DMD participants had lower Max $DF^{Passive}$ than BMD (P<0.001), LGMD (P=0.040), FSHD (P<0.001) and CTRL (P<0.001) groups. CTRL participants had greater Max $DF^{Passive}$ than BMD (P<0.001), LGMD (P<0.001) and FSHD (P=0.006) groups. No other differences were found between groups for Max $PF^{Passive}$ or Max $DF^{Passive}$ (P>0.05, Table 6.2).

ROM^{Active} was 60%, 54%, 58% and 82% smaller in DMD compared to BMD (P=0.002), LGMD (P=0.041), FSHD (P=0.006) and CTRL (P<0.001), respectively. CTRL participants had 55%, 60% and 56% greater ROM^{Active} than BMD (P<0.001), LGMD (P<0.001) and FSHD (P<0.001) groups, respectively. $ROM^{Passive}$ was 49%, 39%, 48% and 66% smaller in the DMD group compared to BMD (P<0.001), LGMD (P=0.026), FSHD (P<0.001) and CTRL (P<0.001) groups, respectively. $ROM^{Passive}$ was 34%, 44% and 35% larger in CTRL compared to BMD (P<0.001), LGMD (P<0.001) and FSHD (P<0.001), respectively. CTRL participants had 42%, 32%, 34% and 34% bigger $ROM^{Active}/ROM^{Passive}$ than DMD (P<0.001), BMD (P<0.001), LGMD (P=0.001) and FSHD (P<0.001) groups, respectively. No other differences were found between groups for ROM^{Active}, $ROM^{Passive}$ or $ROM^{Active}/ROM^{Passive}$ (P>0.05, Table 6.2, Figure 6.1).

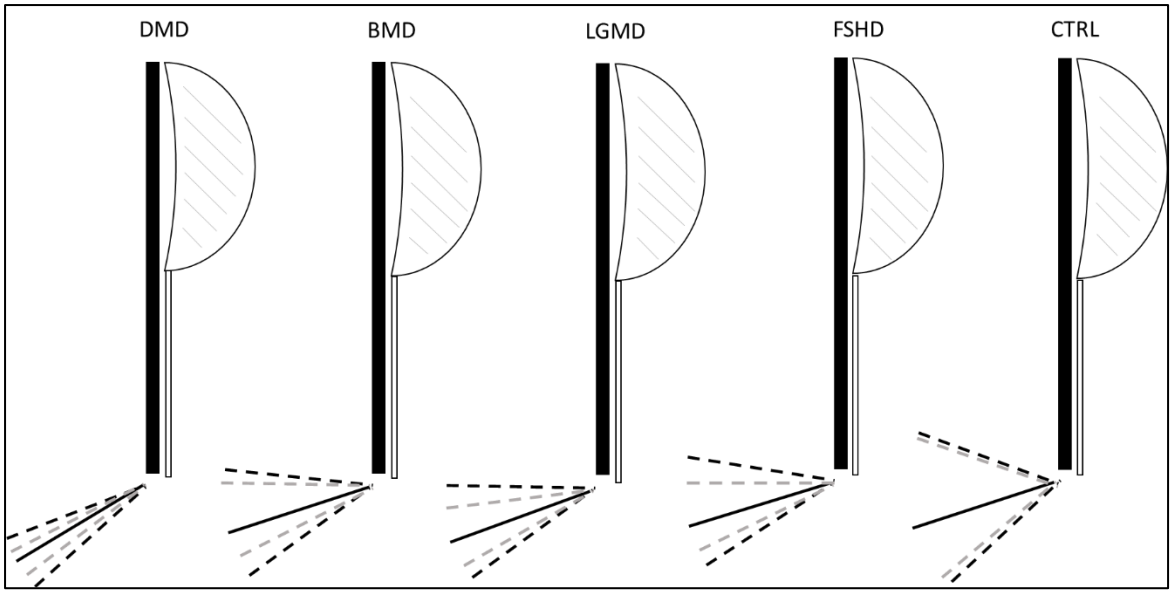


Figure 6.1. Presentation of reported ankle ROM and relative muscle morphology. Key is consistent with that presented in Figure 3.2. In brief ROM measures: Superior black dotted line (- - -) = $DF^{Passive}$; Inferior black dotted line (- -) = $PF^{Passive}$; Superior grey dotted line (- -) = DF^{Active}; Inferior grey dotted line (- - -) – $PF^{Passive}$; Black solid line (—) = Resting Angle. In Brief MTU Morphology: Filled black rectangle (▬) = Tibia; Unfilled black rectangle (▭) = Achilles tendon; Striated half-moon (◡) = Gastrocnemius medialis.

Table 6.2. Range of Motion Assessment

	DMD	BMD	LGMD	FSHD	CTRL
Resting Angle (°)	31.0 (8.3) ^{B,LG,F,C}	17.7 (8.2)	19.8 (10.5)	16.9 (6.1)	17.4 (3.4)
Max PF^{Active} (°)	36.9 (13.7)^{B,F}	27.3 (10.9)^{C}	29.7 (15.7)^{C}	25.3 (8.0)^{C}	39.1 (8.3)
Max DF^{Active} (°)	26.3 (14.4)^{B,LG,F,C}	1.06 (11.8)^{C}	6.70 (10.0)^{C}	-0.23 (10.1)^{C}	-18.7 (2.3)
Max PF^{Passive} (°)	41.5 (14.3)	35.8 (11.4)	35.9 (13.2)	32.1 (9.4)	42.8 (8.9)
Max DF^{Passive} (°)	20.2 (14.2) ^{B,LG,F,C}	-5.71 (10.0)^{C}	0.90 (10.2)^{C}	-8.69 (7.3)^{C}	-20.4 (2.5)
ROM^{Active} (°)	10.6 (4.92) ^{B,LG,F,C}	26.2 (12.8) ^{C}	23.0 (14.6) ^{C}	25.5 (11.1) ^{C}	57.8 (8.6)
ROM^{Passive} (°)	21.3 (9.4)^{B,LG,F,C}	41.5 (13.1) ^{C}	35.0 (14.4) ^{C}	40.7 (9.2) ^{C}	63.1 (9.5)
ROM^{Active}/ROM^{Passive} (%)	52.8 (15.6) ^{C}	62.4 (21.8) ^{C}	60.7 (28.0) ^{C}	60.6 (16.4) ^{C}	91.6 (4.9)

Table 6.2. Range of Motion Assessment. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD – Facioscapulohumeral Muscular Dystrophy, PF^{Active} = Active Plantar-Flexion, DF^{Active} = Active Dorsi-Flexion, $PF^{Passive}$ = Passive Plantar-Flexion, $DF^{Passive}$ = Passive Dorsi-Flexion, ROM^{Active} = Active Range of Motion, $ROM^{Passive}$ = Passive Range of Motion. ^{B} denotes significant difference from BMD, ^{LG} denotes significant difference from LGMD, ^{F} denotes significant difference from FSHD, ^{C} denotes significant difference from CTRL.

6.4.3 Muscle Properties

DMD participants had weaker PFMVC than BMD (47%, P=0.011), FSHD (60%, P<0.001) and CTRL (73%, P<0.001) groups. In addition, CTRL had stronger PFMVC than BMD (50%, P<0.001), LGMD (58%, P<0.001) and FSHD (33%, P=0.016). No other differences were identified between groups for PFMVC (P>0.05; Table 6.3).

Max Passive PF Torque was lower in DMD than BMD (52%, P=0.001), LGMD (43%, P=0.048), FSHD (59%, P<0.001) and CTRL (66%, P<0.001). CTRL had higher Max Passive PF Torque than

BMD (29%, P=0.019), LGMD (40%, P=0.003). DMD had reduced MTJ Displacement than BMD (67%, P=0.001), LGMD (67%, P=0.003), FSHD (75%, P<0.001) and CTRL (84%, P<0.001). CTRL had greater MTJ Displacement than BMD (52%, P<0.001), LGMD (52%, P=0.003) and FSHD (37%, P=0.025; Table 6.3).

GM stiffness was higher in DMD than BMD (29%, P=0.008), LGMD (46%, P<0.001), FSHD (40%, P<0.001) and CTRL (55%, P<0.001). BMD had higher GM stiffness than LGMD (23%, P=0.035) and CTRL (37%, P<0.001). FSHD also had higher GM stiffness than CTRL (25%, P=0.019). No differences were identified between any group for MTU stiffness (P<0.05; Table 6.3).

Table 6.3 Muscle properties

	DMD	BMD	LGMD	FSHD	CTRL
PFMVC (N.m)	17.8 (7.9) ^{B,F,C}	33.4 (13.6)^{C}	28.2 (16.5)^{C}	45.0 (20.6)^{C}	67.0 (13.1)
Max Passive PF Torque (N.m)	8.07 (3.64) ^{B,LG,F,C}	16.8 (7.14) ^{C}	14.2 (3.25) ^{C}	19.5 (7.10)	23.5 (6.08)
MTJ Displacement (cm)	0.25 (0.13) ^{B,LG,F,C}	0.76 (0.46) ^{C}	0.76 (0.29) ^{C}	0.99 (0.47) ^{C}	1.57 (0.40)
GM Stiffness (N.m.cm^{-1})	34.6 (5.89) ^{B,LG,F,C}	24.5 (4.74)^{LG,C}	18.9 (1.68)	20.7 (3.51)^{C}	15.5 (4.52)
MTU Stiffness (N.m.deg^{-1})	0.81 (0.27)	0.74 (0.24)	0.85 (0.27)	0.75 (0.18)	0.65 (0.23)

Table 6.3. Ultrasound and Torque Measures. DMD = Duchenne Muscular Dystrophy, BMD = Beckers Muscular Dystrophy, LGMD = Limb-Girdle Muscular Dystrophy, FSHD = Facioscapulohumeral Muscular Dystrophy, CTRL = Control MTJ = Musculotendinous Junction, PFMVC = Plantar-Flexion Maximal Voluntary Contraction, cm = centimetre, N.m = Newton Metres. ^{B} denotes significant difference from BMD, ^{LG} denotes significant difference from LGMD, ^{F} denotes significant difference from FSHD, ^{C} denotes significant difference from CTRL.

6.4.4 ROM Associations

No associations were identified for any MD group between age or L^{GM} and $ROM^{Passive}$ or ROM^{Active} (P>0.05, Table 6.4).

PFMVC was weakly associated with $ROM^{Passive}$ (r= 0.402, P=0.030) and ROM^{Active} (r= 0.442, P=0.020) in DMD. PFMVC was weakly associated with ROM^{Active} (r= 0.376, P=0.041) in BMD. PFMVC was strongly associated with ROM^{Active} (r= 0.750, P=0.003) in LGMD. PFMVC was weakly associated with ROM^{Active} (r= 0.484, P=0.023), and moderately associated with $ROM^{Passive}$ (r= 0.562, P=0.008) in FSHD (Table 6.4).

MTJ Displacement was moderately associated with ROM^{Active} (r= 0.566, P=0.003) in DMD. BMD showed weak associations of MTJ Displacement with ROM^{Active} (r= 0.376, P=0.041) and $ROM^{Passive}$ (r= 0.487, P=0.007). MTJ Displacement was moderately associated with $ROM^{Passive}$ (r= 0.536, P=0.012) in FSHD (Table 6.4).

Max Passive PF Torque was weakly associated with ROM^{Active} (r= -0.376, P=0.041) and $ROM^{Passive}$ (r= -0.457, P=0.012) in BMD. Max Passive PF Torque was moderately associated with $ROM^{Passive}$ (r= -0.562, P=0.008) in FSHD (Table 6.4).

GM stiffness was weakly associated with ROM^{Active} in DMD (r= -0.407, P=0.032). GM stiffness was weakly associated with ROM^{Active} (r= -0.408, P=0.027) and $ROM^{Passive}$ (r= -0.391, P=0.031) in BMD. MTU Stiffness was weakly associated with ROM^{Active} in LGMD (r= -0.464, P=0.013) and $ROM^{Passive}$ in DMD (r= -0.464, P=0.048, Tale 6.4).

Table 6.4. Active and Passive ROM Associations

	Age	L^{GM}	PFMVC	MTJ Displacement	Max Passive PF Torque	GM Stiffness	MTU Stiffness
ROM^{Active} (°)	-	-	0.442^{D} 0.376^{B} 0.750^{LG} 0.484^{F}	0.566^{D} 0.376^{B}	-0.376^{B}	-0.407^{D} -0.408^{B}	-0.494^{LG}
$ROM^{Passive}$ (°)	-	-	0.402^{D} 0.562^{F}	0.487^{B} 0.536^{F}	-0.457^{B} -0.562^{F}	-0.391^{B}	-0.464^{D}

Table 6.4. Active and Passive ROM Associations. ROM^{Active} = Active Range of Motion, $ROM^{Passive}$ = Passive Range of Motion, L^{GM} = Gastrocnemius Medialis, PFMVC = Plantar-Flexion Maximal Voluntary Contraction, MTJ = Musculotendinous Junction. ^{D} denotes significant association in DMD; ^{B} denotes significant association in BMD; ^{LG} denotes significant association in LGMD; ^{F} denotes significant association in FSHD; - denotes no significant associations.

6.5 Discussion

This chapter assessed ROM in adults with MD compared to CTRL, and investigated previously speculated limiting factors of ROM in adults with MD. As expected, there was a comparative loss of $ROM^{Passive}$ and ROM^{Active} in MD compared to CTRL, and DMD compared to BMD, LGMD and FSHD. Adults with DMD, BMD and FSHD all showed increased GM stiffness compared to CTRL, however interestingly no differences were identified between groups for MTU Stiffness. MTU stiffness, GM stiffness and muscle weakness were found to be associated with limited ROM across MD classifications, the weak-medium associations identified however suggests a combination of muscle properties limits ankle ROM in adults with MD.

The presented ankle $ROM^{Passive}$ appear on the whole, consistent with previous research, with $ROM^{Passive}$ loss compared to CTRL in the present chapter -42°, -22°, -28° and -23° in DMD,

BMD, LGMD and FSHD respectively, compared to -44°, -15°, -47° and -28° reported previously (Johnson et al., 1992). Differences in loss of $ROM^{Passive}$ between the present chapter and that reported previously for LGMD participants, can be explained by the wide range of ages recruited previously 9-82 years (LGMD) (Johnson et al., 1992), in contrast to the homogenous sample in the present chapter of 28-50 years for LGMD. It is possible, particularly within LGMD that the higher reported loss of $ROM^{Passive}$ (-47°) in previous participants (9-82years) represents a much more severe progression of the condition into later life.

The 55% higher GM stiffness in adults with DMD compared to CTRL in the present chapter is consistent with the progressive nature of DMD, where 34% higher GM stiffness was reported previously in children with DMD (Lacourpaille et al., 2015). Furthermore, in the present chapter, increased GM stiffness in adults with DMD, BMD and FSHD appear consistent with the understanding of non-contractile replacement of contractile tissue associated with each of these conditions (Mathur et al., 2010; Løkken et al., 2016). In animal models of DMD, associations have been identified between non-contractile tissue and limited ROM (Garlich et al., 2010), with the assumption that non-contractile tissue is collagenous and would therefore increase the tensile stiffness (Puxkandl et al., 2002). In adults with BMD the contractile properties of the triceps surae have however been shown to remain impaired even when corrected for non-contractile tissue, suggesting a possible change in contractile tissue properties (Løkken et al., 2016), however future investigations are required to quantify the implications of non-contractile tissue on ROM and stiffness in human models. In the present chapter, differences identified between groups for GM stiffness rather than MTU stiffness suggests the impaired movement of the MTJ is a major limitation of ROM in MD, however muscle weakness was associated with all MD for ROM^{Active}, but also $ROM^{Passive}$ for DMD and

FSHD. Therefore, future studies are required to identify methods to maintain muscle strength, and reduce GM stiffness in order to maintain, or improve, ROM.

Adults with BMD, LGMD and FSHD all appear relatively comparable across ROM measures, with limitations in Max DF^{Active} the most prominent finding, despite relatively maintained Max $DF^{Passive}$. Although not measured in the present chapter, DF strength (DFMVC) has been presented previously as a classic area of weakness in FSHD (Emery, 2002), while weaker PFMVC was a consistent association of limited ROM in the present chapter. Issues with ankle strength and Max DF^{Active} are a real concern given reduced functional ability and associated increased fall risk (Spink et al., 2011; Menz et al., 2006). Orthotics can be used to aid DF during gait (Statland and Tawil, 2014), and while restricted, current evidence from exercise training suggests it is safe (Sveen et al., 2008; Sveen et al., 2007). Further studies are required to quantify the effectiveness of exercise training in MD (Voet et al., 2010), and implications on gait and fall risk. The present chapter has demonstrated reduced PFMVC to be associated with limited ROM^{Active}, therefore methods to improve PFMVC, and most likely DFMVC, may help to improve ROM^{Active}, which in turn may help to maintain $ROM^{Passive}$, however future studies should explicitly study this. Only one previous study, in FSHD only, has targeted DFMVC with resistance training however, which reported negative impacts of resistance training on DFMVC (Van der Kooi et al., 2004). Training could alternatively target other lower limb muscles that may respond better to resistance training, thereby improving function and gait (Damiano et al., 2010).

In CTRL populations passive stretching has been shown to reduce GM stiffness by increasing MTJ displacement (Morse et al., 2008), and passive stretching is actively encouraged in MD as a potential method of improving $ROM^{Passive}$ (UK, 2016). Passive stretching however has

previously been shown to be less effective than night splints in the long term maintenance of ROM in children with DMD (Hyde et al., 2000). No measure of ROM was reported however, nor was there a non-treatment group against which to compare passive stretching. The long-term use of passive stretching may be beneficial to reduce progression of limited $ROM^{Passive}$, there are however no reports of the effectiveness of stretching and physiotherapy in adults with MD.

In DMD the resting ankle angle is a more PF position, consistent with equinus deformity and static positioning issues identified previously (Bushby et al., 2010; Williams et al., 1984), likely caused by long term immobilisation in a seated position resulting in shortening of L^{MTU} (Herbert and Crosbie, 1997; Morse et al., 2015). In DMD difficulties in ROM^{Active} and Max DF (active and passive) would appear consistent with muscle weakness (Chapter 3) and shorter L^{GM} (Morse et al., 2015), although specific associations of DF ROM were not reported in this chapter. This highlights the necessity of good static positioning of the foot in adults with DMD in as neutral position as possible, as poor positioning in PF could further reduce L^{GM} (Spector et al., 1982). Reductions in L^{GM} from sustained static positioning in PF may also reduce the active and passive force-length properties of the GM (Maganaris, 2003), therefore further reducing the ability to actively move through ROM.

6.6 Conclusion

In conclusion, the present chapter has quantified limited ankle ROM in four classifications of adults with MD, identifying muscle weakness and increased GM stiffness as consistent associations of ROM. Further research is required to establish the mechanisms of increased GM stiffness in adults with MD, which would appear consistent with the understanding of non-contractile replacement of contractile tissue. Following the identification of ROM and its

associations with stiffness and weakness, methods to reduce stiffness and increase muscle strength associated with ankle ROM are required to reduce fall risk and the loss of independence in adults with MD. Therefore Chapter 7 will investigate the acute responses of physiotherapy on ROM and muscle stiffness properties in adults with DMD.

Chapter 7

Physiotherapy in Adults with Duchenne Muscular Dystrophy: Acute Responses

7.1 Abstract

Background

Physiotherapy is currently a best-practice method of care to maintain function in Duchenne muscular dystrophy (DMD). Experimental data of the effectiveness of physiotherapy is however limited to children with DMD. Given the progressive nature of DMD and increases in life expectancy, it is important to quantify the effectiveness of physiotherapy in adults with DMD to improve measures of joint range of motion (ROM) without further decreasing muscle strength in the short term.

Methods

This chapter employed a prospective cohort design with a sample comprising of 14 adult males with DMD. Participants were tested at baseline (visit 1) and then pre and post physiotherapy (Pre physio and Post physio) on visit 2. Due to no CTRL sample, MDC was calculated, based on the SEM between baseline and pre-physio. Maximum active and passive measures were taken of dorsiflexion (Max DF^{Active} and Max $DF^{Passive}$), plantarflexion (Max PF^{Active} and Max $PF^{Passive}$) and total range of motion (ROM^{Active} and $ROM^{Passive}$). Displacement of the myotendinous junction (MTJ) through $ROM^{Passive}$, of the gastrocnemius medialis (GM) were determined by B-mode ultrasound. GM stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the distal displacement of the MTJ. Muscle-tendon unit (MTU) stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the ankle angle. Isometric maximal voluntary contraction (MVC) was assessed during plantar-flexion (PFMVC) using a load cell. Intraclass Correlation Coefficients were calculated between Visit 1 and Visit 2, and used to calculate SEM and MDC. Freidman's test was used to assess differences from baseline, pre-physio and post-physio, with a Bonferroni correction.

Results

Max $DF^{Passive}$ increased post-physio by 3.1° (15%) and exceeded the MDC criterion (2.24°). Post-Physio ROM^{Active} showed no significant change from pre-physio. Post-physio $ROM^{Passive}$ increased by 4.8° (19%) from pre-physio and exceeded the MDC criterion (3.58°). Compared to pre-physio, post-physio MTU stiffness decreased by 0.23 $N.m \cdot deg^{-1}$ (27%) and exceeded the MDC criterion (0.10 $N.m \cdot deg^{-1}$).

Conclusion

Physiotherapy is an effective method to acutely increase ankle $ROM^{Passive}$ in adults with DMD, with no negative effects on muscle strength. The increase in $ROM^{Passive}$ and Max $DF^{Passive}$ was likely attributable to reduction in MTU stiffness, which has previously been shown to limit ROM in adults with DMD. Given the improvements in ROM it would appear daily passive stretching on the ankle would be beneficial for adults with DMD, and should form part of their multi-disciplinary care.

7.2 Introduction

Chapter 5 quantified the limitations of ankle ROM, GM stiffness and MTU stiffness, specifically, in adults with DMD (hereafter ROM will refer to ankle DF-PF ROM only). Extensive research has assessed the impacts of pharmacological interventions, such as corticosteroid treatments, on delaying the onset and progression of such condition characteristics in children with DMD (Bonifati et al., 2000; Daftary et al., 2007; Escolar et al., 2011; Fenichel et al., 1991). Muscular Dystrophy UK (MDUK) emphasises the standing of the Chartered Society of Physiotherapists that long-term muscle function should be maintained to ensure mobility and QoL in adults with DMD (Campaign, 2008). In adults with DMD, best practice physiotherapy is limited to a combination of passive stretching and mobility exercises (hereafter referred to as physiotherapy) and is compatible in even the most severely affected individuals (Stockley et al., 2010). Despite physiotherapy being known to be effective for reducing the stiffness of the GM and MTU in cerebral palsy (Theis et al., 2013; Palmer et al., 1988), there is no evidence for the effectiveness physiotherapy for improving ROM, or the viscoelastic properties of the MTU, in adults with DMD.

Limited ROM has been historically reported in children with DMD (Johnson et al., 1992) and broad multi-component methods, including passive stretching and the use of orthotics and night-splints, have been widely recommended for maintaining ROM (Bushby et al., 2010; McDonald, 1998). The long-term use of these methods has been shown as effective for delaying the loss of ROM and maintaining ambulation in children with DMD (Vignos and Archibald, 1960; Vignos et al., 1963; Hyde et al., 2000). Given the progressive and degenerative nature of DMD, resulting in loss of ambulation in adolescents, it is important to assess the effectiveness of physiotherapy in adults with DMD, who have developed further limited ROM and weakness (Chapter 3 and 5).

While the outcomes of delaying the loss of ambulation and ROM following longitudinal passive stretching, have been previously reported in children with DMD (Vignos and Archibald, 1960; Vignos et al., 1963), maintained ambulation as an outcome measure is however redundant in adults with DMD (Morse et al., 2018), and the mechanisms associated with maintenance of ROM remain unreported. In Chapter 5, ROM^{Active} was associated with muscle weakness, and ROM determined by a Principal Investigator passively moving their foot to its maximum ($ROM^{Passive}$) was associated with MTU Stiffness. In adults without MD, passive stretching has previously been shown to reduce MTU stiffness (Morse et al., 2008) and increase $ROM^{Passive}$ (McNair and Stanley, 1996), however this response has not been investigated in adults with DMD. Decreases in MTU stiffness following stretching, have however, been associated with short-term compromises in muscle strength (Behm et al., 2001; Cramer et al., 2005; Fowles et al., 2000). Given the known muscle weakness reported in adults with DMD (Chapter 3), it is also important to determine whether physiotherapy can lead to further short-term decrements in muscle strength.

This chapter aims to quantify the acute effect of physiotherapy on 1) Range of Motion Measures, 2) Stiffness Properties Associated with the ankle as identified in Chapter 6and 3) Muscle Strength, in adults with DMD.

This chapter hypothesises that $ROM^{Passive}$ and $DF^{Passive}$ will both increase following Physiotherapy, and be attributable to reductions in GM Stiffness and MTU Stiffness. In addition, this chapter hypothesises that PFMVC will also be reduced following Physiotherapy.

7.3 Methods

Full details of methods can be found in Chapter 3, in brief: This chapter employed a prospective cohort design with a sample comprising of 14 adult males with DMD. Participants

were tested at baseline (visit 1) and then pre and post physiotherapy (Pre physio and Post physio) on visit 2. Due to no CTRL sample, MDC was calculated, based on the SEM between baseline and pre-physio. Maximum active and passive measures were taken of DF (Max DF^{Active} and Max $DF^{Passive}$), PF (Max PF^{Active} and Max $PF^{Passive}$) and total ROM (ROM^{Active} and $ROM^{Passive}$). Displacement of the GM MTJ through $ROM^{Passive}$, of the gastrocnemius mediali was determined by B-mode ultrasound. GM stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the distal displacement of the MTJ. MTU stiffness was calculated as passive plantar-flexor torque during a $DF^{Passive}$ movement, relative to the ankle angle. PFMVC was measured using a load cell.

7.3.1 Statistical Analysis

All analyses were performed using IBM SPSS Statistics v21 software with a critical level of statistical significance set at 5%. Test for parametricity (Shapiro-Wilks and Levenes) were performed upon all variables. For repeated measures analysis of ROM and muscle properties, all variables were revealed as non-parametric. All data is presented as mean (SD) except for physio frequency which is presented as median (range).

Ambulatory status and physiotherapy frequency are presented for descriptive purposes. ICC were calculated between Visit 1 and Visit 2, and used to calculate SEM and MDC (See above equations). Freidman's test was used to assess differences from baseline, pre-physio and post-physio, with a Bonferroni correction. Where relevant, comparisons are presented with P values, with changes in DF and PF expressed in degrees from pre-physio, with changes in ROM (active and passive) and muscle properties expressed as relative change (%) from pre-physio.

7.4 Results

Participant characteristics are presented below in Table 7.1.

Table 7.1. Participant Characteristics, Anthropometrics, Body Composition and Care

	DMD
n	14
Age (years)	23.7 (6.1)
Body Mass (Kg)	76.3 (19.2)
Height (cm)	172.5 (4.4)
LBM (Kg)	49.8 (9.9)
Ambulatory	0/14
Physiotherapy Frequency (visits per month)	3 (1-4)

Table 7.1. Participant Characteristics, Anthropometrics, Body Composition and Care. DMD = Duchenne Muscular Dystrophy, LBM = Lean Body Mass, cm = centimetres, Kg = Kilograms.

7.4.1 Range of Motion

MDC criteria was met and statistically significant changes observed pre-physio to post-physio for an increased resting angle ($P<0.001$), an increased Max $DF^{Passive}$ ($P<0.001$) and an increased $ROM^{Passive}$ ($P<0.001$, Table 7.2).

MDC criteria was not met, albeit statistical significance was observed, from pre-physio to post-physio for Max $PF^{Passive}$ (Table 7.2).

MDC criteria was met, however statistical significance was not observed, from pre-physio to post-physio for Max PF^{Active} (Table 7.2).

Neither MDC criteria nor statistical significance was met from pre-physio to post-physio for Max DF^{Active} and ROM^{Active} (Table 7.2).

Table 7.2. Range of Motion measures at Baseline and Pre Physio and Post Physio

	DMD					
	Baseline	**Pre-Physio**	**Post-Physio**	**Δ Pre- Physio Post-Physio**	**MDC**	**ICC**
Resting Angle (°)	30.9 (13.9)	30.8 (13.7)	34.8 (12.6)*	4.0	1.21†	.999
Max PF^{Active} (°)	37.1 (14.6)	37.5 (14.6)	39.3 (13.0)	1.8	1.28†	.999
Max DF^{Active} (°)	26.9 (14.6)	27.6 (14.0)	28.7 (14.3)	1.1	2.56	.996
Max PF^{Passive} (°)	41.4 (15.3)	41.2 (15.5)	42.8 (15.3)*	1.6	2.32	.997
Max DF^{Passive} (°)	20.9 (14.7)	20.9 (14.6)	17.8 (14.6)*	3.1	2.24†	.997
ROM^{Active} (°)	10.1 (4.5)	9.93 (8.7)	10.6 (5.2)	0.67	2.10	.972
ROM^{Passive} (°)	20.5 (9.4)	20.3 (8.7)	25.1 (9.0)*	4.8	3.58†	.981

Range of Motion measures at Baseline, Pre-Physio and Post-Physio. DMD = Duchenne Muscular Dystrophy, Max PF^{Active} = Maximum Active Plantar-Flexion, Max DF^{Active} = Maximum Active Dorsi-Flexion, Max PF^{Passive} = Maximum Passive Plantar-Flexion, Max DF^{Passive} = Maximum Passive Dorsi-Flexion, ROM^{Active} = Active Range of Motion, ROM^{Passive} = Passive Range of Motion. ‡ denotes P<0.05 at Pre-Physio from Baseline.* denotes P<0.05 difference at Post-Physio from Pre-Physio. † denotes the Post-Physio change from Pre-Physio is greater than the MDC.

7.4.2 Muscle Properties

MDC criteria was met and statistically significant changes observed pre-physio to post-physio for decreased MTU Stiffness (P<0.001, Table 7.3).

MDC criteria was not met, albeit statistical significance was observed, from pre-physio to post-physio for PFMVC, MTJ Displacement and GM Stiffness (Table 7.3).

Neither MDC criteria nor statistical significance was met from pre-physio to post-physio for Max Passive PF Torque (Table 7.3).

Table 7.3. Muscle Properties at Baseline, Pre-Physio and Post-Physio.

	DMD					
	Baseline	**Pre-Physio**	**Post-Physio**	**Δ Pre- Physio Post-Physio**	**MDC**	**ICC**
PFMVC (N.m)	17.4 (7.7)	17.5 (8.0)	16.2 (7.5)*	1.3	2.81	.984
Max Passive PF Torque (N.m)	7.59 (3.5)	7.68 (3.6)	7.97 (3.4)	0.29	1.07	.988
MTJ Displacement (cm)	0.23 (0.13)	0.23 (0.13)	0.26 (0.12)*	0.03	0.06	.975
GM Stiffness ($N.m \cdot cm^{-1}$)	35.2 (6.6)	35.6 (6.3)	32.3 (4.7)*	3.3	5.4	.914
MTU Stiffness ($N.m \cdot deg^{-1}$)	0.83 (0.28)	0.84 (0.32)	0.61 (0.18)*	0.23	0.10†	.984

Muscle Properties at Baseline, Pre-Physio and Post-Physio. DMD = Duchenne Muscular Dystrophy, MTJ = Myotendinous Junction, PFMVC = Plantar-Flexion Maximal Voluntary Contraction, cm = centimetre, N.m = Newton Metres. ‡ denotes P<.05 at Pre-Physio from Baseline.* denotes P<.05 difference at Post-Physio from Pre-Physio. † denotes the Post-Physio change from Pre-Physio is greater than the MDC.

7.5 Discussion

The main findings of the present chapter is that physiotherapy appears an effective method to acutely increase ankle $ROM^{Passive}$ in adults with DMD. This increased $ROM^{Passive}$ is likely attributable to the observed decreases in MTU stiffness following physiotherapy. In addition, no negative impacts of physiotherapy on muscle strength were identified in the present chapter.

The outcomes from the present chapter suggests that physiotherapy is an effective method to acutely increase $ROM^{Passive}$ in adults with DMD, with no negative effects on PFMVC or ROM^{Active}. Increases in $ROM^{Passive}$ post-physio are consistent with increases in $ROM^{Passive}$ reported previously in clinical and non-clinical populations following physiotherapy

interventions (Radford et al., 2006; Wiktorsson-Moller et al., 1983; Theis et al., 2013; Gao et al., 2011). The 15% increase in Max $DF^{Passive}$ in the present chapter is comparable to other acute responses to passive interventions presented previously in adults without MD (9-26%) (Morse et al., 2008; Wiktorsson-Moller et al., 1983). Furthermore, the present chapter shows physiotherapy as an effective method to reduce MTU stiffness consistent with previous research (Morse et al., 2008), which is evidenced in the outcome measure itself, but also in the increase in $ROM^{Passive}$ and shift of resting angle into greater PF.

The decrease in MTU stiffness observed in the present chapter (a correlate of DF ROM in Chapter 6), is consistent with previous studies on the impact of passive interventions in CTRL groups (Morse et al., 2008). These decreases in MTU stiffness are normally attributable to decreases in GM and tendon stiffness, with previous research showing acute increases in tendon stiffness and reduction in GM stiffness following passive interventions (Nakamura, 2011; Morse et al., 2008). In the present chapter, post-physio GM stiffness did not decrease sufficiently from pre-physio to meet the MDC criterion, while tendon stiffness could not be calculated, as previous methods use cadaveric equations which are incomparable with adults with DMD (Grieve, 1978). Given that the impairments of DMD are associated with degradation of muscle quality, whereby contractile tissue is replaced with non-contractile tissue, therefore it is deemed that tendon stiffness may be less relevant in this population. The observed decrease in MTU stiffness were however, apparent with no change in Max Passive PF Torque, changes could therefore be attributed to an increase in stretch tolerance (Magnusson et al., 1997), rather than necessarily changes in muscle properties (Magnusson et al., 2000). It is important to acknowledge however, that small decreases in both muscle and tendon stiffness may have contributed to the increased ROM, but did not reach MDC criteria. Future work is required to determine the respective GM stiffness and tendon stiffness

properties and their change in response to physiotherapy, these may be more apparent and methodologically measurable in BMD, a comparably milder condition (Huml, 2015).

The present chapter has focussed on the acute responses of limited ankle ROM in adults with DMD to physiotherapy, given its presentation as a characteristic of DMD (Archibald and Vignos Jr, 1959; Vignos et al., 1963). The improvement in $ROM^{Passive}$ is consistent with current guidelines for care of adults with DMD (MDUK), that physiotherapy can improve ROM, and should be part of the multi-disciplinary approach to maintaining function and potentially limiting the progressive loss of passive mobility described in adults with DMD (Bushby et al., 2010; McDonald, 1998). While limited ROM of the ankle may be a characteristic of DMD (Archibald and Vignos Jr, 1959), future work should assess the impact of physiotherapy on upper limb function, which could have a greater impact on activities of daily living in this population given their non-ambulant nature (Bartels et al., 2011). Similarly, the effects of physiotherapy on milder or more functional forms of MD such as BMD and FSHD are required given the limitations in $ROM^{Passive}$ identified in Chapter 5, as it may be able to delay functional impairments and loss of ambulation (Brooke et al., 1989; Vignos and Archibald, 1960).

7.6 Conclusion

To conclude, physiotherapy is an effective method to acutely increase ankle ROM in adults with DMD, with no negative effects on muscle function, however further work is required to quantify its long-term effects. The increases in $ROM^{Passive}$ in the current chapter are attributed to reductions in MTU stiffness from physiotherapy, which was identified as an associate of limited ankle $ROM^{Passive}$ in Chapter 5. Given the improvements in ROM it would appear daily passive stretching on the ankle would be beneficial and should form part of the multi-disciplinary care for adults with MD.

Chapter 8

Muscle Size, Strength and Physical Activity in Adults with Muscular Dystrophy: A One Year Follow Up

8.1 Abstract

Background

Muscular dystrophy (MD) is characterised by progressive muscle wasting and weakness, few studies however, have assessed longitudinal changes in lower limb function and body compositions in adult MD populations. Physical activity (PA) is encouraged in MD to maintain health and function; however, its association with longitudinal changes also remains unreported.

Methods

This Chapter included 15 adults with Duchenne MD (DMD) and 11 adults with Becker's MD (BMD). Participants were assessed at baseline and at 12 months. Body fat (%) and lean body mass (LBM) were measured using bioelectrical-impedance. Gastrocnemius medialis (GM) anatomical cross-sectional area (ACSA) was determined using B-mode ultrasound. Isometric maximal voluntary contraction (MVC) was assessed during plantar-flexion (PFMVC) and knee extension (KEMVC). Physical activity was measured for seven continuous days using tri-axial accelerometry, and was expressed as daily average minutes being physically active (TPA^{mins}) or average daily percentage of waking hours being sedentary (Sedentary Behaviour). Additionally, 10m walk time was assessed. For repeated measures Paired T-tests and Wilcoxon signed rank tests, for parametric and non-parametric respectively, were used to identify changes, with a Bonferroni correction. Linear, Quadratic and Cubic regressions are used to best model changes in body composition and muscle strength in relation to age and changes in TPA^{mins}, with the best fit model presented.

Results

Compared to baseline, 12 month LBM decreased by -5% in DMD and Body Fat% increased by 4% in BMD. No other changes were identified for body composition. One BMD participant lost ambulation between baseline and 12 months. Compared to baseline, PFMVC and KEMVC

decreased in DMD by -19% and -14%. No differences were identified in KEMVC or PFMVC at 12 months compared to baseline in BMD. Compared to baseline 10m walk time increased in ambulant BMD by 13% (P=0.005). In BMD quadratic polynomial regressions best identified relationships for TPA^{mins} change with PFMVC change (R^2=0.585) and KEMVC change (R^2=0.532).

Conclusions

Changes in DMD appear consistent with the progressive nature of the condition, with -14% and -19% weaker PFMVC and KEMVC after 12 months, respectively. Within BMD, 12 month changes in PFMVC and KEMVC although not significant, were best explained by changes physical activity. Changes in LBM in DMD and Body Fat% in BMD were both masked by non-significant changes in body mass, furthering the need for specific monitoring of body composition.

8.2 Introduction

Chapters 4-6 have focussed on cross-sectional relationships of clinical features associated with MD, the present Chapter will assess the longitudinal changes in muscle weakness, muscle morphology and body characteristics. The progressive nature of DMD means it has been a focus of a wide range of cross-sectional and longitudinal studies quantifying the progression of the condition (hereafter termed “natural history”), and evaluating the impact of steroid treatment (Akima et al., 2012; Bendixen et al., 2014; Elliott et al., 2012; Jansen et al., 2013; Kohler et al., 2005; C. McDonald, R. Abresch, et al., 1995).

‘Clinical endpoints’ are used to describe natural history, such as the 6-minute walk test (6MWT) which has shown declines in function with age (Mayhew et al., 2007; Henricson et al., 2013; McDonald et al., 2010). The scope of functional tasks such as the 6MWT are however limited, as children with DMD typically lose ambulation by the age of 12, rendering the 6MWT

and other functional measures redundant from this point as a clinical outcome measure (Morse et al., 2018).

Broad conclusions can be drawn on the natural history of strength in DMD through the use of the MRC% and MMT (Florence et al., 1992; Mendell and Florence, 1990). These subjective, manual assessment methods have previously been identified as lacking sensitivity to quantify changes (Florence et al., 1992). Indeed, when using MMT or MRC%, annual declines of KEMVC are reported as -5% in children with DMD (5-13 years) (C. McDonald, R. Abresch, et al., 1995), and 1.2-2% in non-ambulant DMD (13-24 years) (C. McDonald, R. Abresch, et al., 1995; Steffensen et al., 2002), whereas when using more sensitive measures of strength assessment such as dynamometers, annual declines of KEMVC are reported as -15% in children with DMD (8-12 years) (Henricson et al., 2013). The use of more stringent measures of strength assessment, such as dynamometers, however are largely inaccessible given the severe muscle weakness and contractures associated with adults with DMD as discussed in Chapter 2. Despite DMD being progressive in nature, natural history descriptions of quantified lower limb muscle strength in adults with DMD are yet to be reported. Given the improvements in health care, particularly cardiac and respiratory, life expectancy is increasing in DMD, with many now living well into adulthood (Bettolo et al., 2016). It is therefore essential for greater understanding of the progression of DMD in this older age group, and to provide comparative norms, using relevant and accessible methods, for future longitudinal assessments of steroid therapy or other intervention studies which may be relevant to this population (Bettolo et al., 2016; Rahbek et al., 2005).

In comparison to DMD, BMD is perceived as a milder, yet more variable condition (Emery, 2002). The loss of ambulation sometimes does not occur in BMD until middle age (C. M.

McDonald et al., 1995), and the maintenance of physical function is related to the amount of dystrophin present (Bello et al., 2016), with lower limb muscle strength previously associated with physical function ((Alfano et al., 2013)Chapter 3). In terms of natural history in BMD, a single MMT assessment of KEMVC has been conducted, with annual declines reported of -1.2% (C. M. McDonald et al., 1995), no studies however have quantified the progression of lower limb muscle strength in adults with BMD using sensitive methods.

The focus of natural history studies in DMD and BMD has understandably been muscle strength (Henricson et al., 2013), with limited description of changes in body composition or muscle size. LBM have been identified as a determinant of strength and function in children with DMD (Palmieri et al., 1996; Skalsky et al., 2009) and adults with BMD (Chapter 3). While pseudohypertrophy (increased muscle size without relative increase in strength) is well documented in children with DMD (Beenakker et al., 2002; Vohra et al., 2015; Wokke et al., 2014), the limited investigations into muscle size in adults with DMD suggest it may not persist in adulthood (Morse et al., 2015); longitudinal changes in muscle size and LBM remain unreported however, in adults with DMD and BMD. Similarly, increased fat mass has previously been cited as a common co-morbidity in MD (Zanardi et al., 2003), and noted as higher in non-ambulant adults with BMD in a recent paper (Jacques et al., 2017). Continual assessment, and understanding, of body composition changes of both lean and fat mass is essential for not only their implications on function, but also the much broader impacts on health and wellbeing (Hogan, 2008; Davidson and Truby, 2009).

Despite shortcomings in natural history studies reporting subjective strength measures in children with DMD and adults with BMD, both conditions certainly progressive in nature (C. M. McDonald et al., 1995; C. McDonald, R. Abresch, et al., 1995). Previous cross sectional

studies (in children with DMD) and Chapter 3 (in adults with BMD) have shown associations between age and strength (Mathur et al., 2010; Bello et al., 2016), with lower muscle strength leading to a loss of function (Alfano et al., 2013; Bendixen et al., 2014). The rate of this decline may however be influenced by PA. Lower levels of PA in adults with BMD, FSHD and LGMD has been linked to lower levels of bone health and grip strength (Morse, 2016). In adults with BMD, Chapter 3 showed group variance in KEMVC could be explained by PA, while adolescents with DMD taking part in structured assisted cycling have previously been shown to maintain function compared to those that did not (Jansen et al., 2013). In addition, adults with FSHD have shown that increased PA (steps) maintained contractile tissue more than those who did not increase PA (Ferguson et al., 2016). It is therefore possible that PA levels may be a determinant of the rate of the decline in KEMVC in adults with BMD.

This chapter aims to: 1) To quantify changes, from a one year follow up, in body composition, muscle morphology, muscle strength and physical activity levels in adults with Duchenne and Becker's MD 2) Identify the impact of changes in physical activity on body composition and muscle strength.

It is hypothesised that 1) declines will be significant in both DMD and BMD, for lower limb strength, GM ACSA and LBM; and 2) PA may account for some of the variance in lower limb strength change in BMD.

8.3 Methods

Full details of methods can be found in Chapter 3, in brief: this Chapter included 15 adults with DMD and 11 adults with BMD. Participants were assessed at baseline and at 12 months. Body fat (%) and LBM were measured using bioelectrical-impedance. GM ACSA was determined using B-mode ultrasound. KEMVC and PFMVC were measured using methods

replicative of QMT. PA was measured for seven continuous days using tri-axial accelerometry, and was expressed as daily average minutes being physically active (TPA^{mins}) or average daily percentage of waking hours being sedentary (Sedentary Behaviour). Additionally, 10m walk time was assessed.

8.3.1 Statistical Analyses

All analyses were performed using IBM SPSS Statistics v21 software with a critical level of statistical significance set at 5% and all data presented as mean (SD). Between group differences for baseline measures have been described previously (Chapter 3), with the present chapter interested in differences from baseline-12 months, therefore statistical analysis has been performed on baseline to 12month changes only (within group), with baseline values presented for clarity. Test for parametricity (Shapiro-Wilks and Levenes) were performed upon all variables, for repeated measures DMD BM, height, BMI, LBM and PFMVC were parametric, while for BMD height, body fat%, Lean Mass, GM ACSA, PFMVC, SB% and TPA^{mins} were parametric, all other variables were non-parametric. Ambulatory status is presented as a characteristic and no statistical analysis was performed on it.

For repeated measures Paired T-tests and Wilcoxon signed rank tests, for parametric and non-parametric respectively, were used to identify changes, with a Bonferroni correction. Where relevant, comparisons are presented with P values, and the relative change (%) baseline.

Stepwise Multiple Linear Regression was used to identify the best predictors of PFMVC change from GM ACSA Change, LBM Change and Baseline PFMVC. Linear, Quadratic and Cubic regressions are used to best model changes in body composition and muscle strength in relation to age and changes in TPA^{mins}, with the best fit model presented.

8.4 Results

8.4.1 12 Month Changes

Comparisons have only been made between baseline and 12 months data, as differences between DMD and BMD were systematically addressed in Chapter 4**.** Compared to baseline, 12 month LBM and GM ACSA decreased by -5% (P=0.002) and -8% (P=0.012) respectively, in DMD. There was no significant change in GM ACSA or LBM in BMD (P>0.05). In BMD, compared to baseline, Body Fat% increased by 4% (P=0.009) after 12 months. One BMD participant lost ambulation between baseline and 12 months. No other differences were identified between baseline and 12 months for measures of anthropometric, body composition or muscle size for DMD or BMD (Table 8.1, P>0.05).

Compared to baseline, PFMVC and KEMVC decreased in DMD by -19% and -14%, respectively (P=0.002; P=0.003). There was no difference in KEMVC or PFMVC compared to baseline in BMD. Compared to baseline 10m walk time increased in ambulant BMD by 13% (P=0.005). No other differences were identified between baseline and 12 months for any other measures (Table 8.1, P<0.05).

Table 8.1. 12 Month changes in body composition, muscle size, lower limb strength and physical activity

	DMD			BMD		
	Baseline	12-Months	%Change	Baseline	12-Months	%Change
N		15			12	
Age (years)	24.2 (6.1)	25.2 (6.1)	-	44.1 (12.6)	45.1 (12.6)	-
Stature (cm)	172.0 (4.3)	172.0 (4.3)	-	178.9 (6.2)	178.9 (6.2)	-
Body Mass (Kg)	73.1 (14.6)	71.4 (14.5)	-2%	84.4 (15.1)	85.1 (16.4)	0%
BMI (Kg/m^2)	25.5 (4.1)	22.7 (7.5)	-11%	26.4 (4.9)	26.6 (5.4)	0%
Body Fat (%)	33.3 (6.7)	33.0 (7.0)	-1%	28.8 (8.8)	29.8 (8.9)*	3%
LBM (Kg)	47.6 (7.7)	45.0 (6.4)*	-5	59.3 (7.8)	58.8 (8.1)	-1%
Ambulatory	0/15	0/15	-	9/12	8/12	-
GM ACSA (cm^2)	23.3 (16.5)	21.4 (16.3)*	-8%	29.7 (18.4)	26.6 (14.4)	-10%
PFMVC (N.m)	16.7 (6.8)	13.6 (6.3)*	-19%	35.7 (11.3)	33.2 (12.2)	-7%
KEMVC (N.m)	12.6 (8.8)	10.8 (7.0)*	-14%	97.7 (64.3)	83.9 (56.2)	14%
SB%	96.4 (4.5)	98.5	2%	83.4 (7.2)	83.9 (6.3)	0%
TPA^{mins}	13.5 (16.1)	7.17 (8.9)	-47%	123.1 (57.6)	120.4 (50.7)	-2%
10m Walk (s)†		-		11.0 (2.9)	12.7 (3.9)*	15%

Table 8.1. One year changes in MD strength, physical activity and function. DMD = Duchenne Muscular Dystrophy; BMD = Beckers Muscular Dystrophy; PFMVC = Plantar-Flexion Maximum Voluntary Contraction; KEMVC = Knee Extension maximum Voluntary Contraction; SB% = Percentage of waking hours in Sedentary Behaviour; TPA^{mins} = Minutes of Total Physical Activity; m = metres; s = seconds; † Ambulant BMD only (n=8); *denotes significant changes from baseline.

8.4.2 Regressions

Stepwise Multiple Linear Regression identified a model containing baseline PFMVC, GM ACSA change and LBM change best predicted PFMVC Change in DMD (R^2=0.582, P=0.019).

No relationship was identified for DMD using any regression model for age or TPA^{mins} change with change in PFMVC, KEMVC, LBM or body fat% ($P>0.05$). No relationships were identified for either DMD or BMD using any regression model for age with change in PFMVC, KEMVC, LBM or body fat%, or TPA^{mins} change with change in LBM or body fat % ($P>0.05$).

In BMD quadratic polynomial regressions best identified relationships for TPA^{mins} change with PFMVC change ($R^2= 0.585$, $P=0.019$, Figure 8.1A) and KEMVC change ($R^2= 0.532$, $P=0.033$, Figure 8.1B). No relationships were identified DMD using any regression model for TPA^{mins} PFMVC change or KEMVC change ($P>0.05$).

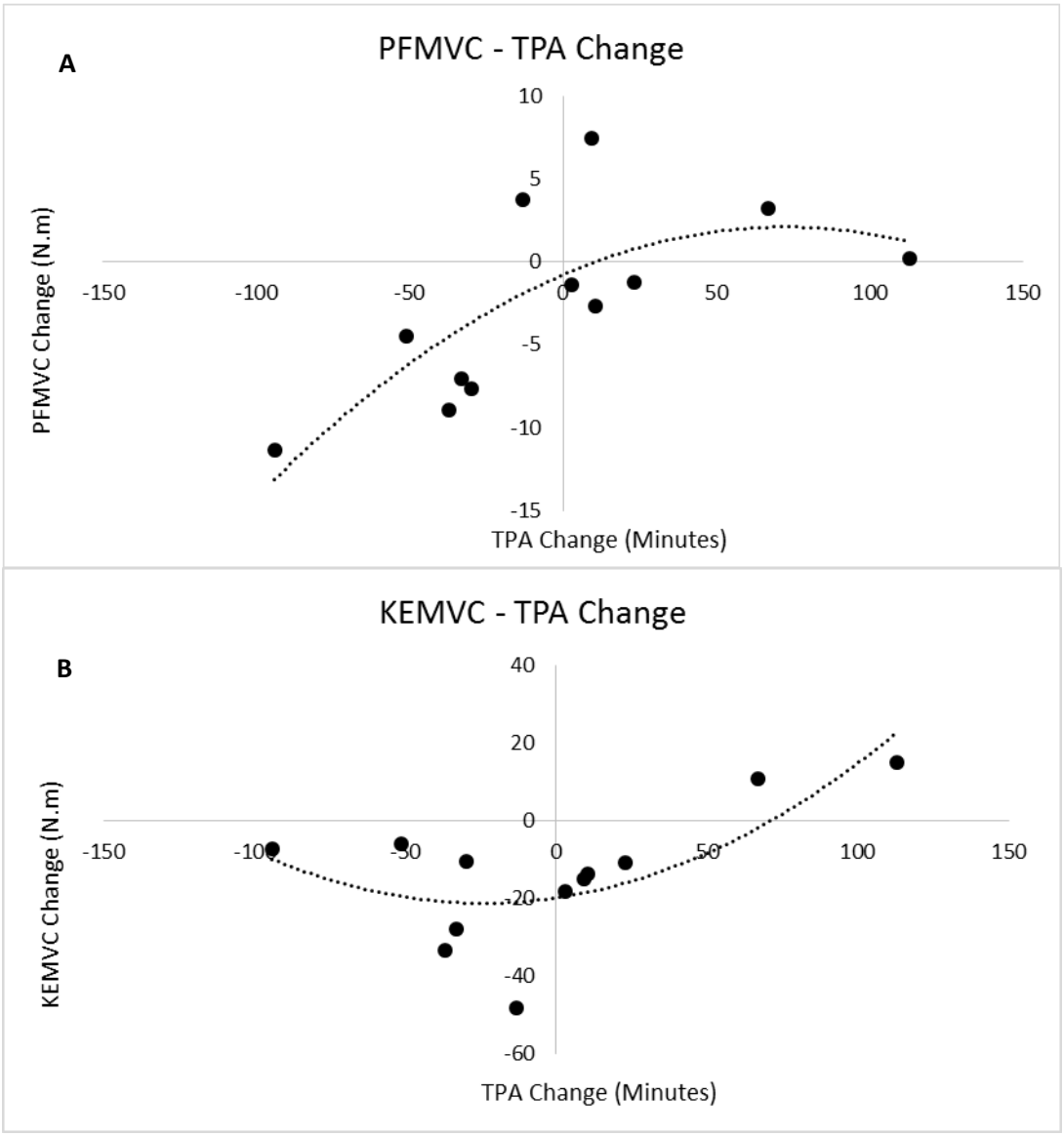


Figure 8.1. BMD strength change and physical activity change relationships; A. PFMVC change and TPA^{mins} change in BMD; B. KEMVC change and TPA^{mins} change in BMD. PFMVC = Plantar Flexion Maximal Voluntary Contraction, N.m = Newton Metres, TPA = Total Physical Activity, KEMVC = Knee Extension Maximal Voluntary Contraction.

8.5 Discussion

The progression of DMD is well described in children (C. McDonald, R. Abresch, et al., 1995; Henricson et al., 2013), while in Chapter 3 cross-sectional muscle strength was presented in adults with DMD and BMD; the present chapter however presents longitudinal changes in lower limb muscle strength, muscle size and body composition in adults with BMD and DMD.

In the present chapter, after 12 months, LBM, GM ACSA, PFMVC and KEMVC decreased in DMD, whereas in BMD there was no change in any measure, other than body fat (%) which was increased. Although there was no significant decrease in strength within BMD, the variance in the 12-month change of PFMVC and KEMVC was attributable to the variance in PA change.

The -14% decline in KEMVC in adults with DMD in the present chapter is consistent with the -15% decline previous reported over a similar timeframe in children with DMD (Henricson et al., 2013). These declines in KEMVC are in contrast to the -2% and -1.2% reported in non-ambulant children and adolescents with DMD, respectively (Steffensen et al., 2002; Henricson et al., 2013). This discrepancy can be attributed to the greater sensitivity of the methods used in the present chapter to quantify changes in KEMVC, rather than subjective measures of MMT or MRC% (Hogrel et al., 2007; Cuthbert and Goodheart, 2007). In adults with BMD we observed no significant change in KEMVC or PFMVC, likely due to greater variance, however the quantified declines of -14% KEMVC and -7% PFMVC remain noteworthy and statistical trends of decline were still evident ($P<0.1$). Previous research has utilised MMT to monitor changes in strength over a 10 year period (C. M. McDonald et al., 1995), reporting -1.2% annual declines in KEMVC per year. Despite the declines of PFMVC and KEMVC in the present BMD participants being higher than those reported previously, the fact that they did not reach significance reflects the large variability of the condition progression (C. M. McDonald et al., 1995).

Decreases in LBM and GM ACSA in DMD, but not in BMD, appear to be consistent with the classical definition of DMD being the more progressive condition (Huml, 2015), and likely reflects the greater dystrophin protein defect in DMD compared to BMD (Bello et al., 2016).

The non-ambulatory nature and high SB% recognised in this population (Chapter 3) may also contribute to the increased progression. The reductions in GM ACSA appear consistent with findings that pseudohypertrophy (increased calf size) is primarily a paediatric characteristic (Beenakker et al., 2002; Jones et al., 1983), and that muscle size in the calf region decreases in adulthood (Morse et al., 2015). This is furthered by the inclusion of GM ACSA, LBM change and baseline PFMVC in the multiple linear regression model for change in PFMVC, further evidence for the relationships between body composition and muscle function.

The increase in body fat% in BMD (+4%) in the present chapter after 12 months appears consistent with previous research in which the author previously identified excess weight gain as an issue in BMD, especially in non-ambulant individuals (Jacques et al., 2017). The relative increase in body fat% in BMD compared to DMD may be due to the fact that BMD remain relatively functional with a greater level of physical independence (Lue et al., 2009), compared DMD (Morse et al., 2018), who require assistance in the preparation and consumption of food, therefore BMD may maintain nutritional control, and a possible poor diet. Monitoring and management of food intake may be easier and more structured in DMD (Pane et al., 2006). The stable BM did however, mask changes in body composition with decreased LBM decreased in DMD and increased Body Fat% in BMD; reaffirming the need for body composition monitoring in these conditions.

BMD participants that maintained or increased PA levels showed a relative increase or maintenance of muscle strength compared to those that decreased PA levels. Increased PA has previously been attributed to decelerating fatty infiltration of muscles in FSHD (Ferguson et al., 2016). Based on the present relationship between PA and declines in muscle strength, it seems reasonable to suggest interventions that increase PA (equivalent to > 1.5 METs) in

adults with BMD may benefit muscle strength, and mitigate some of the declines associated with the condition. Future work needs to investigate the benefits of increasing PA, and to further identify psycho-somatic and/or social barriers and facilitators of PA and patterns of SB in this population (Phillips et al., 2009).

8.6 Conclusion

In conclusion, the present data describes natural history changes in body composition, strength and PA in adults with DMD and BMD. Changes in DMD appear consistent with the understanding of the condition, with -14-19% weaker PFMVC and KEMVC, consistent with previous research (Mok et al., 2010; Morse et al., 2015; Henricson et al., 2013). Change in DMD PFMVC was best explained by changes in LBM, GM ACSA and Baseline PFMVC. Within BMD 12 month changes in PFMVC and KEMVC although not significant, were be best explained by change in TPA^{Mins}. Changes in LBM in DMD and Body Fat% in BMD were both masked by non-significant changes in BM, furthering the need for specific monitoring of body composition.

Chapter 9

General Discussion

9.1 Overview

As described in Chapter 1, there is extensive literature into the genetics of MD (Angelini, 2013; Deconinck and Dan, 2007; Huml, 2015), as well as the health, function and pharmacological interventions in children with DMD (Guglieri et al., 2008; Angelini, 2007; C. McDonald, R. Abresch, et al., 1995). The understanding of health and function in adults with MD is by comparison, poorly reported (Pandya et al., 2018; Kilmer et al., 1995; C. M. McDonald et al., 1995). The advances in cardiac and respiratory care have improved life expectancy in DMD (Eagle et al., 2002) and revealed a lack of descriptive data on the physical function of adults with DMD (McDonald and Mercuri, 2018; Rahbek et al., 2005). Similarly, in milder conditions such as BMD, LGMD and FSHD, the limited research has typically focussed on ambulant and relatively functional participants, which while valuable, does not reflect the large numbers that are non-ambulant (Løkken et al., 2016; Skalsky et al., 2008). The present thesis aimed to address the following in adults with MD:

Chapter 4: To investigate the relationship between muscle strength and size; Establish the relationship between muscle size and strength with objective measures of physical activity, with implications for the maintenance of muscle function in MD.

Chapter 5: Compare the self-reported QoL of adults with DMD, BMD, LGMD and FSHD, and a non-MD CTRL group; Present and compare between groups measures of Muscle Strength, Activities of Daily Living, Fatigue, Pain, Self-Efficacy and BMI; Identify associations between QoL domains and Muscle Strength, Activities of Daily Living, Fatigue, Pain, Self-Efficacy and BMI.

Chapter 6: Compere ROM^{Active} and $ROM^{Passive}$ in adults with MD and CTRL; Compare levels of MTU and GM stiffness in adults with MD and CTRL; Identify associations of ROM with measures of muscle weakness, stiffness and muscle length.

Chapter 7: Quantify the acute effect of physiotherapy on 1) Range of Motion Measures, 2) Stiffness Properties Associated with the ankle as identified in Chapter 7 and 3) Muscle Strength, in adults with DMD.

Chapter 8: Quantify changes, from a one year follow up, in body composition, muscle morphology, muscle strength and physical activity levels in adults with DMF and BMD; Identify the impact of changes in physical activity on body composition and muscle strength in adults with BMD and DMD.

9.2 Main Findings

Progressive muscle weakness and limited ROM are clinical features associated with MD (Huml, 2015; Emery, 2002), but have been limited in their presentation in adults with MD, with much focus in children with DMD (Brooke et al., 1989; Bakker et al., 2002). These two clinical features of MD have been quantified in this thesis, and identified as the main themes for discussion, for which their associations and implications are discussed below, with an overview presented in Appendix 10.

This thesis has presented cross-sectional comparisons of lower limb muscle strength in adults with MD (Chapter 4), and 12 month changes in lower limb strength in DMD (-14-19%) and BMD (Chapter 8). The presented findings appear largely consistent with the previous findings from children with DMD (Mathur et al., 2010; Lott et al., 2014; Vohra et al., 2015) and the limited reports in adults with BMD, LGMD and FSHD (Skalsky et al., 2008; Løkken et al., 2016). The importance of lower limb muscle strength is evident by the respective associations

identified with 10m walk time in ambulant adults with MD (Chapter 4), QoL domains of Physical Function and Social Function in BMD (Chapter 5), and ROM^{Active} measures consistent across adults with MD (Chapter 6).

Where the work in this thesis is particularly novel, is that PA, measured over 7 days with an accelerometer, and could explain variance in muscle weakness in both the cross-sectional presentation (Chapter 4) and longitudinal changes, in adults with BMD (Chapter 8). In addition, while functional performance of 10m walk could be predicted by lower limb strength, PA was the best predictor of 10m walk time in ambulant adults with MD (Chapter 4). These findings suggest that PA is important for maintaining muscle function in adults with MD, consistent with the recommendations from MDUK (2014). Furthermore, the increased SB presented in this thesis, in addition with increased body fat % reported in adults with MD, and negative associations between BMI and domains of QoL, has further raised concerns of negative implications of SB on physical and mental health and wellbeing in adults with MD (Chapter 4 and 5).

Progressive muscle weakness is a defining clinical feature of MD (Huml, 2015) and has previously been associated with QoL in children with DMD (McDonald et al., 2010), however, prior to this thesis muscle weakness had not been associated with measures of QoL in adults with MD. Within adults with MD, despite KEMVC being associated with the performance of functional tasks (10m walk time) in ambulant adults with MD in Chapter 4 and reported previously in adults with BMD (Alfano et al., 2013), in Chapter 5 KEMVC was only associated with the Physical Function and Social Function domains of QoL in BMD. By comparison, the Physical Function domain was associated with ADL in DMD, BMD and FSHD, suggesting independence and ownership of activities is of greater importance to adults with MD, possibly

due to the high proportion of non-ambulant adults with MD in this thesis (Chapter 3). Furthermore, while muscle weakness had limited associations with domains of QoL, BMI (LGMD), Pain (BMD and FSHD) and Self-Efficacy (DMD) were all consistent associates of QoL domains, while Fatigue (DMD, BMD and FSHD) was the most consistent associate of QoL (Chapter 5). These findings suggest a shift in focus is required in adults with MD, particularly given the largely non-ambulant sample in the present thesis, from impairment to perceptions, to improve QoL.

Ankle $ROM^{Passive}$ in Chapter 6 appears consistent with that previously reported in adults with MD (Johnson et al., 1992), where this thesis is novel is in the presentation of $ROM^{Passive}$ in adults with DMD, and the quantification of ROM^{Active} in adults with DMD, BMD, LGMD and FSHD. Adults with DMD are extremely limited in their $ROM^{Passive}$, with evidenced equinus deformity, while adults with BMD, LGMD and FSHD all appear relatively comparable across ROM measures, however, limited DF^{Active} is the most prominent finding, despite relatively maintained $DF^{Passive}$. The limitations identified in DF^{Active} have raised concerns of potential increased fall risk (Menz et al., 2006). In addition, Chapter 6 identified possible contributing factors of limited ankle ROM, with PFMVC associated with ROM^{Active}, while GM stiffness and MTU stiffness were associated with limited $ROM^{Passive}$, however the mild associations evidenced suggest it is a combination of factors that limit ROM in adults with MD. Physiotherapy however, appears to be an effective method to acutely increase $ROM^{Passive}$ in adults with DMD (Chapter 7). Chapter 7 showed no negative effects were identified from physiotherapy on ROM^{Active} or PFMVC, however decreases in MTU Stiffness were identified, and attributed for the increase in $ROM^{Passive}$.

9.3 Clinical Implications

Progressive muscle weakness is arguably the most prominent clinical feature of MD (Emery, 2002; Huml, 2015). This thesis has identified that the variance in progressive muscle weakness, and in particular functional measures, in ambulant adults with MD has been shown to be partly explainable PA (Chapter 4). In addition, the longitudinal changes in muscle strength in BMD were also explainable in changes of PA (Chapter 8). Maintenance of muscle strength in MD appears important in ambulant adults with MD: In BMD, KEMVC was associated with domains of QoL (Chapter 5), while PFMVC was associated consistently across MD with ROM^{Active} (Chapter 6). Maintenance of lower limb muscle strength may help to maintain ambulation, and reduce the possible fall risk associated with lower muscle strength and limited DF^{Active} (Campbell et al., 1989). Furthermore, in adults with LGMD, BMI was a consistent associate of QoL (Chapter 5), therefore methods to reduce body fat (Tremblay et al., 1990; Tremblay et al., 2010), such as PA, would likely improve BMI and may improve QoL. Therefore, this thesis provides support, consistent with MDUK (Campaign, 2014), for the encouragement of PA when possible, particularly in ambulant adults with MD in order to maintain lower limb function and health.

In non-ambulant adults with MD, adults with DMD showed a negative association between SB% and LBM (Chapter 4), suggesting any method of physical movement, and interrupting prolonged bouts of SB, is important for this population. This builds on previous work from Jansen et al. (2013), who showed maintenance of function through assisted exercise protocols, and suggests similar methods of assisted arm ergometry and passive exercise could prove important to maintain LBM in adults with DMD. Beyond physical function, Chapter 5 suggests a shift in focus is required in non-ambulant adults with MD, and adults with DMD in particular, from physical function to measures of perception. For example, in adults with DMD

no associations with QoL were identified using KEMVC, however ADLs were associated with domains of QoL, suggesting independence and ownership of activities and social behaviours, such as being able to use a phone, becomes much more important. Furthermore, identification of pain and fatigue as consistent measures associated with QoL (Chapter 5), across MD, but likely influenced by the largely non-ambulatory nature of the sample in this thesis, furthers this suggested shift in focus, and that pain and fatigue should be consistently monitored, and a focus of condition progression. Potential interventions that are known to reduce pain and fatigue in other clinical conditions include acupuncture (Vickers et al., 2012), physiotherapy (Jansen et al., 2011; Smart et al., 2016), and where possible, PA (as has been applied in FSHD (Voet et al., 2014)) may be applied in adults with MD and could possibly improve QoL. While unlikely to impact a non-ambulant individual with MDs QoL, evidence in Chapter 6 also suggests physiotherapy is an effective measure to acutely improve the clinical feature of limited $ROM^{Passive}$ in adults with DMD. Although speculative, the effectiveness of physiotherapy measured in Chapter 6 suggests physiotherapy should be encouraged regularly in adults with MD, as a method of ROM maintenance in non-ambulant individuals, and as a method of maintaining ankle properties for ambulation in ambulant individuals with MD.

9.4 Limitations

A wide range of techniques have previously been used to describe muscle strength, body composition and muscle size in clinical populations (Martone et al., 2017; Blauwhoff-Buskermolen et al., 2017; Yang et al., 2017). Limitations of previous methods used for muscle strength assessment have been systematically described in Chapter 2, however in brief; the most stringent methods of strength assessment are limited to the most functional participants, while the least stringent (MMT and MRC%) which are commonly used, to assess

the most physically impaired, lack objectivity and sensitivity (Cuthbert and Goodheart, 2007; Escolar et al., 2001; Løkken et al., 2016). By comparison, the methods of QMT in the present thesis are shown to be reliable within MD (Chapter 1: PFMVC - Between day ICC 0.832-.984, Within day ICC 0.911-.985; KEMVC – Between day ICC 0.956-.991, Within day ICC 0.973-.992). In addition, the coefficient of variation of the CTRL KEMVC was 34%, which is comparative with the normative database for quantitative muscle testing ((Hogrel et al., 2007); n = 122, CV = 29%, mean difference = 4.3 N.m).

Similarly, BIA is necessary as an alternative to more stringent measures of body composition in MD where mobility is limited (Mok et al., 2010). BIA has been used extensively in sarcopenia research (Makizako et al., 2017; Heber et al., 1996) and shown as valid in obese and underweight individuals (Pateyjohns et al., 2006; Sun et al., 2005; Lupoli et al., 2004), a degree of error is however likely to be introduced within MD given the fat infiltration of muscle tissue (Sun et al., 2005). Based on previous validity data, BIA would underestimate the body fat percentage (BF%) in the present overweight MD participants and underestimate BF% in normal weight CTRL participants (Sun et al., 2005). When corrected, based on the values in Chapter 4, previously established, BF% would be 18% in CTRL (measured = 18.2%), and 33.8% in MD (measured = 30.8%). Therefore, despite the error associated with comparing BF% when using BIA, there is no meaningful impact on the conclusions drawn from the presented results. Similarly, the use of ultrasound for assessment of ACSA, although consistent with those previously reported, is likely to be overestimated in those individuals with high levels of muscle fat fraction (FF%)(Løkken et al., 2016). Based on the work of Løkken et al. (2016), the actual GM contractile area of ambulant BMD participants is ~23% less than the measured ACSA, in contrast the GM contractile area of the CTRL is 11% less than the measured ACSA.

Based on this estimated value the contractile area in ambulant BMD (n= 10) is 15.7 cm^2 and CTRL is 13.0 cm^2 in the present study, consistent with the comparisons made by (Løkken et al., 2016). It is therefore likely that the present GM ACSA is higher in the MD participants due to the presence of pseudohypertrophy (Jones et al., 1983). Future work is required to determine whether the measurement of muscle area is meaningful within adults with MD as it may not reflect any functional measure due to the level of non-contractile material contained within the muscle compartment (as observed within the lack of correlation between ACSA and strength in the present study, and previously by Løkken et al. (2016)).

Although there are shortcomings to some methodologies used in this thesis, the use of transportable and adaptable equipment has allowed for 60 adults with MD encompassing a wide range of functional ability to be assessed. Up to 60% of MD participants in this thesis would have been unable to participate had DEXA or MRI been used for body composition and non-contractile muscle percentage, commonly referred to as FF%, assessment. The present authors suggest the use of adaptable equipment to encompass wide functional ranges in future studies, with the use of methods such as MRI to assess muscle FF% in sample subsets when possible and practical.

As stated consistently throughout this thesis, and above, all testing was designed for the most severely impaired (adults with DMD), and then replicated on more functional and less impaired participants for consistency and to allow comparisons. The GM however, studied in the thesis, is bi-articular and therefore is influenced by the joint angle of both the knee and ankle (van Ingen Schenau et al., 1987). The use of a seated position for testing in this thesis, consistent with the body position of adults with DMD in power wheelchairs, with hip and knee angles at 90°, will predispose the GM to a shortened position (Maïsetti et al., 2012; Gao et al.,

2009). This long-term seated position, and its predisposition of a shortened L^{GM}, has been attributed to the shortening of L^{GM} noted in adults with DMD (Spector et al., 1982; Morse et al., 2015). This shortened L^{GM}, likely alters the length-tension relation of the non-ambulatory MD participants, compared to those who are ambulatory. For consistency, PFMVC should be measured at optimum angles in all participants given the shift in ROM observed in Chapter 6. The implications for the data presented here are likely minimal, as the actual force produced in the most severely affected, non-ambulatory participants was negligible, and measurement of PFMVC at optimum angle would accentuate differences between the most-to-least impaired. In addition, the ROM of the ambulatory participants were similar, meaning that the PFMVC measured at 90°, would reflect the same region of their ankle force-length relation.

Chapter 7 was unable to use a CTRL comparison of no intervention, as it was deemed unethical to remove or reduce care for participants (Johnson et al., 1992). Therefore, the use of MDC was used in adjunction with statistical analysis to determine changes in ankle ROM and muscle properties (Hoch et al., 2012; Ries et al., 2009; Steffen and Seney, 2008; Fulk and Echternach, 2008). Participants of BMD, LGMD and FSHD were excluded from this chapter and analysis as their comparatively increased lower limb muscle strength, and some participants' maintained ambulation, could increase the SEM of assessments techniques, therefore increasing MDC. By comparison, the lower limbs of adults with DMD are severely impaired, and all participants are long-term wheelchair users; therefore, there is likely no internal or external influences on the relevant variables.

9.5 Future Research

This thesis has presented data in adults with MD broadly, adults with DMD specifically have been identified as a population for being under-reported (McDonald and Mercuri, 2018).

Further research is required to understand and document the health and implications within this population (Pandya et al., 2018). Collaborations are required between research institutions and clinicians to improve the understanding and care for this population (Birnkrant et al., 2018).

This thesis has identified limited PA in adults with MD, and presented implications on health and function, future research needs to build on these findings to identify methods of improving and facilitating PA (Chapter 4). The identified cross sectional relationships between muscle strength and PA in ambulant adults with MD, and PA influencing the progression of muscle weakness in BMD, identified in Chapter 4, suggests PA is a viable method to maintain physical function. Future research is required to identify dose-response relationships and implications on condition progression (Ferguson et al., 2016), SB behaviours, barriers to PA, and impacts of PA interventions on health, such as body fat%. Furthermore, BMI was associated with QoL in LGMD, therefore in conjunction with PA, greater nutritional management systems are required to reduce weight gain following loss of ambulation.

Beyond the implications of PA on physical health, PA has previously been shown to reduce perceived fatigue in adults with FSHD (Voet et al., 2014), future work is required to identify other methods of alleviating fatigue, but also other associates of QoL identified in the present thesis (Chapter 5). This thesis has shown pain to be consistently reported in adults with MD, however evidence of effective interventions to reduce pain in MD remains limited. Physiotherapy and acupuncture are two proposed methods (Morís et al., 2017; Urtizberea et al., 2003), and have been shown effective in other conditions (Vickers et al., 2012), however their effectiveness for reducing pain remains unreported in MD.

ROM assessment for BMD, LGMD and FSHD evidenced limited DF^{Active}, even when $DF^{Passive}$ was relatively maintained. The limited DF^{Active} raises concerns of increased fall risk (Menz et al., 2006). Future research is required to identify methods to maintain and improve functionality of DF in adults with MD, but also the implications on fall risk in these populations. A comprehensive battery of functional measures on reported falls and balance would help to determine effective future interventions.

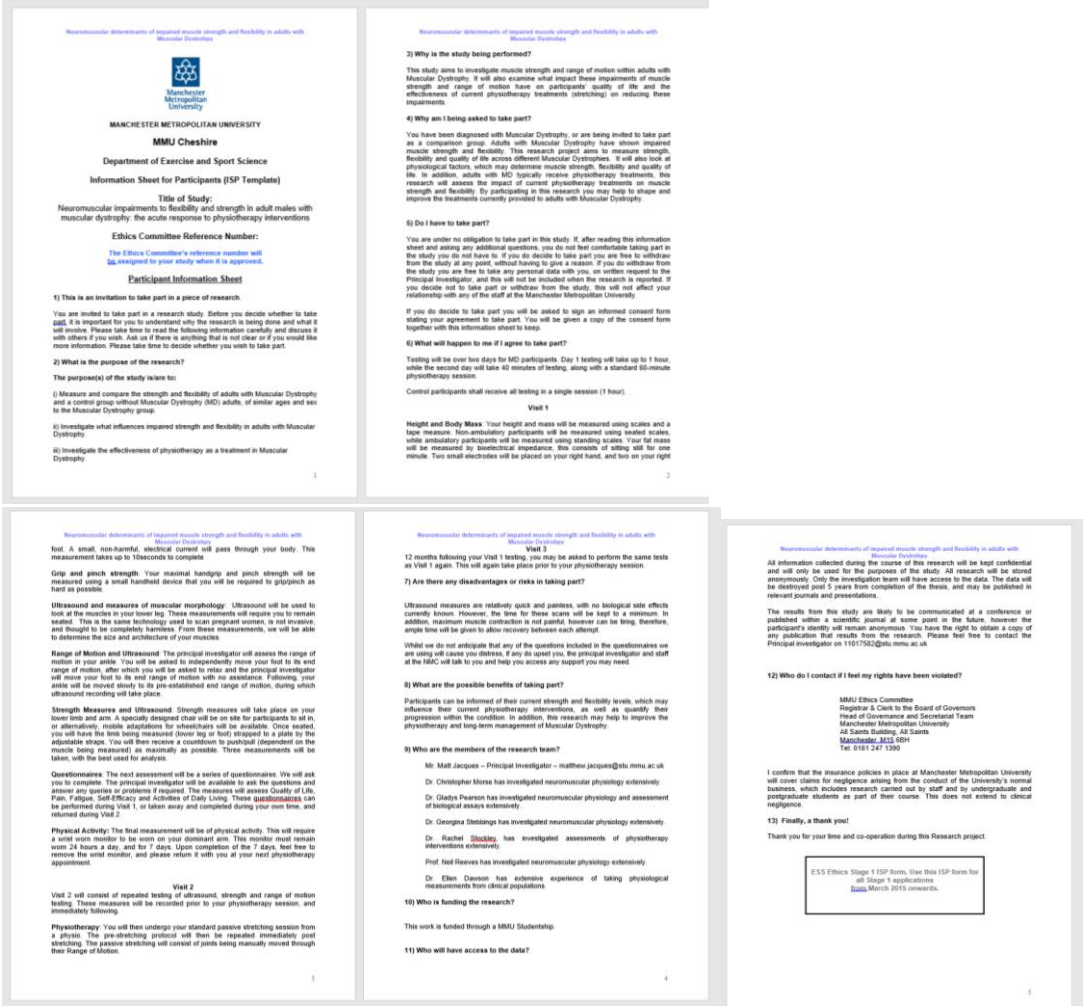
9.6 Conclusions

This thesis has provided a wide range of health and function data in adults with MD. In particular, this thesis has expanded understanding of muscle strength in adults with MD, with what appears to be the first quantified measures of lower limb muscle strength in adults with DMD, as well as the first CTRL compared PFMVC in adults with FSHD, and KEMVC in adults with BMD and LGMD, respectively. The presentation, association and progression of lower limb muscle strength measures have been made in respective chapters.

This thesis should aid clinicians and researchers working as a reference point of function and health in adults with MD, from cross-sectional understanding of strength, body composition and PA, to the progression and implications of these measures. Similarly, this thesis has provided evidence for focussed future interventions, identifying methods to improve PA in adults with MD, reduce pain and fatigue while maintaining independence to improve QoL; while also presenting physiotherapy as an effective acute method to improve ankle $ROM^{Passive}$ in adults with DMD.

Appendices

Appendix 1 – Participant Information Sheet



Neuromuscular determinants of impaired muscle strength and flexibility in adults with Muscular Dystrophy

MANCHESTER METROPOLITAN UNIVERSITY

MMU Cheshire

Department of Exercise and Sport Science

Information Sheet for Participants (ISP Template)

Title of Study:
Neuromuscular impairments to flexibility and strength in adult males with muscular dystrophy: the acute response to physiotherapy interventions

Ethics Committee Reference Number:

The Ethics Committee's reference number will be assigned to your study when it is approved.

Participant Information Sheet

1) This is an invitation to take part in a piece of research.

You are invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether you wish to take part.

2) What is the purpose of the research?

The purpose(s) of the study is/are to:

i) Measure and compare the strength and flexibility of adults with Muscular Dystrophy and a control group without Muscular Dystrophy (MD) adults, of similar ages and sex to the Muscular Dystrophy group.

ii) Investigate what influences impaired strength and flexibility in adults with Muscular Dystrophy.

iii) Investigate the effectiveness of physiotherapy as a treatment in Muscular Dystrophy.

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3) Why is the study being performed?

This study aims to investigate muscle strength and range of motion within adults with Muscular Dystrophy. It will also examine what impact these impairments of muscle strength and range of motion have on participants' quality of life and the effectiveness of current physiotherapy treatments (stretching) on reducing these impairments.

4) Why am I being asked to take part?

You have been diagnosed with Muscular Dystrophy, or are being invited to take part as a comparison group. Adults with Muscular Dystrophy have shown impaired muscle strength and flexibility. This research project aims to measure strength, flexibility and quality of life across different Muscular Dystrophies. It will also look at physiological factors, which may determine muscle strength, flexibility and quality of life. In addition, adults with MD typically receive physiotherapy treatments, this research will assess the impact of current physiotherapy treatments on muscle strength and flexibility. By participating in this research you may help to shape and improve the treatments currently provided to adults with Muscular Dystrophy.

5) Do I have to take part?

You are under no obligation to take part in this study. If, after reading this information sheet and asking any additional questions, you do not feel comfortable taking part in the study you do not have to. If you do decide to take part you are free to withdraw from the study at any point, without having to give a reason. If you do withdraw from the study you are free to take any personal data with you, on written request to the Principal Investigator, and this will not be included when the research is reported. If you decide not to take part or withdraw from the study, this will not affect your relationship with any of the staff at the Manchester Metropolitan University.

If you do decide to take part you will be asked to sign an informed consent form stating your agreement to take part. You will be given a copy of the consent form together with this information sheet to keep.

6) What will happen to me if I agree to take part?

Testing will be over two days for MD participants. Day 1 testing will take up to 1 hour, while the second day will take 40 minutes of testing, along with a standard 60-minute physiotherapy session.

Control participants shall receive all testing in a single session (1 hour).

Visit 1

Height and Body Mass: Your height and mass will be measured using scales and a tape measure. Non-ambulatory participants will be measured using seated scales, while ambulatory participants will be measured using standing scales. Your fat mass will be measured by bioelectrical impedance, this consists of sitting still for one minute. Two small electrodes will be placed on your right hand, and two on your right

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foot. A small, non-harmful, electrical current will pass through your body. This measurement takes up to 10seconds to complete

Grip and pinch strength: Your maximal handgrip and pinch strength will be measured using a small handheld device that you will be required to grip/pinch as hard as possible.

Ultrasound and measures of muscular morphology: Ultrasound will be used to look at the muscles in your lower leg. These measurements will require you to remain seated. This is the same technology used to scan pregnant women, is not invasive, and thought to be completely harmless. From these measurements, we will be able to determine the size and architecture of your muscles.

Range of Motion and Ultrasound: The principal investigator will assess the range of motion in your ankle. You will be asked to independently move your foot to its end range of motion, after which you will be asked to relax and the principal investigator will move your foot to its end range of motion with no assistance. Following, your ankle will be moved slowly to its pre-established end range of motion, during which ultrasound recording will take place.

Strength Measures and Ultrasound: Strength measures will take place on your lower limb and arm. A specially designed chair will be on site for participants to sit in, or alternatively, mobile adaptations for wheelchairs will be available. Once seated, you will have the limb being measured (lower leg or foot) strapped to a plate by the adjustable straps. You will then receive a countdown to push/pull (dependent on the muscle being measured) as maximally as possible. Three measurements will be taken, with the best used for analysis.

Questionnaires: The next assessment will be a series of questionnaires. We will ask you to complete. The principal investigator will be available to ask the questions and answer any queries or problems if required. The measures will assess Quality of Life, Pain, Fatigue, Self-Efficacy and Activities of Daily Living. These questionnaires can be performed during Visit 1, or taken away and completed during your own time, and returned during Visit 2.

Physical Activity: The final measurement will be of physical activity. This will require a wrist worn monitor to be worn on your dominant arm. This monitor must remain worn 24 hours a day, and for 7 days. Upon completion of the 7 days, feel free to remove the wrist monitor, and please return it with you at your next physiotherapy appointment.

Visit 2

Visit 2 will consist of repeated testing of ultrasound, strength and range of motion testing. These measures will be recorded prior to your physiotherapy session, and immediately following.

Physiotherapy: You will then undergo your standard passive stretching session from a physio. The pre-stretching protocol will then be repeated immediately post stretching. The passive stretching will consist of joints being manually moved through their Range of Motion.

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Visit 3

12 months following your Visit 1 testing, you may be asked to perform the same tests as Visit 1 again. This will again take place prior to your physiotherapy session.

7) Are there any disadvantages or risks in taking part?

Ultrasound measures are relatively quick and painless, with no biological side effects currently known. However, the time for these scans will be kept to a minimum. In addition, maximum muscle contraction is not painful, however can be tiring, therefore, ample time will be given to allow recovery between each attempt.

Whilst we do not anticipate that any of the questions included in the questionnaires we are using will cause you distress, if any do upset you, the principal investigator and staff at the MMC will talk to you and help you access any support you may need.

8) What are the possible benefits of taking part?

Participants can be informed of their current strength and flexibility levels, which may influence their current physiotherapy interventions, as well as quantify their progression within the condition. In addition, this research may help to improve the physiotherapy and long-term management of Muscular Dystrophy.

9) Who are the members of the research team?

Mr. Matt Jacques – Principal Investigator – matthew.jacques@stu.mmu.ac.uk

Dr. Christopher Morse has investigated neuromuscular physiology extensively.

Dr. Gladys Pearson has investigated neuromuscular physiology and assessment of biological assays extensively.

Dr. Georgina Stebbings has investigated neuromuscular physiology extensively.

Dr. Rachel Stockley has investigated assessments of physiotherapy interventions extensively.

Prof. Neil Reeves has investigated neuromuscular physiology extensively.

Dr. Ellen Dawson has extensive experience of taking physiological measurements from clinical populations.

10) Who is funding the research?

This work is funded through a MMU Studentship.

11) Who will have access to the data?

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Neuromuscular determinants of impaired muscle strength and flexibility in adults with Muscular Dystrophy

All information collected during the course of this research will be kept confidential and will only be used for the purposes of the study. All research will be stored anonymously. Only the investigation team will have access to the data. The data will be destroyed post 5 years from completion of the thesis, and may be published in relevant journals and presentations.

The results from this study are likely to be communicated at a conference or published within a scientific journal at some point in the future, however the participant's identity will remain anonymous. You have the right to obtain a copy of any publication that results from the research. Please feel free to contact the Principal investigator on 11017582@stu.mmu.ac.uk

12) Who do I contact if I feel my rights have been violated?

MMU Ethics Committee
Registrar & Clerk to the Board of Governors
Head of Governance and Secretariat Team
Manchester Metropolitan University
All Saints Building, All Saints
Manchester, M15 6BH
Tel: 0161 247 1390

I confirm that the insurance policies in place at Manchester Metropolitan University will cover claims for negligence arising from the conduct of the University's normal business, which includes research carried out by staff and by undergraduate and postgraduate students as part of their course. This does not extend to clinical negligence.

13) Finally, a thank you!

Thank you for your time and co-operation during this Research project.

ES5 Ethics Stage 1 ISP form. Use this ISP form for all Stage 1 applications from March 2015 onwards.

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Appendix 2 – Control Recruitment Poster

Appendix 3 – Participant Consent Form

Manchester Metropolitan University — Cheshire —

Department of Exercise and Sport Science

Informed Consent Form

Manchester Metropolitan University — Cheshire —

(Both the investigator and participant should retain a copy of this form)

Name of Participant:

Supervisor/Principal Investigator: Matthew Jacques

Project Title: Neuromuscular Determinants of Impaired muscle Strength and Range of Motion in Adults with Muscular Dystrophy

Ethics Committee Approval Number: 23.12.15 (i)

Participant Statement

I have read the participant information sheet for this study and understand what is involved in taking part. Any questions I have about the study, or my participation in it, have been answered to my satisfaction. I understand that I do not have to take part and that I may decide to withdraw from the study at any point without giving a reason. Any concerns I have raised regarding this study have been answered and I understand that any further concerns that arise during the time of the study will be addressed by the investigator. I therefore agree to participate in the study.

It has been made clear to me that, should I feel that my rights are being infringed or that my interests are otherwise being ignored, neglected or denied, I should inform the Registrar and Clerk to the Board of Governors, Head of Governance and Secretariat Team, Manchester Metropolitan University, All Saints Building, All Saints, Manchester, M15 6BH, Tel: 0161 247 1390 who will undertake to investigate my complaint.

I confirm that I have had the following exposure to radiation in the last 12 months (please add a total number in each box (or '0' where none)):

Dental x-ray	Whole body x-ray	CT-scan	DEXA scan	Long Haul Flight (4Hrs +)	Others

Signed (Participant) _____ Date _____

Signed (Investigator) _____ Date _____

Parental or guardian consent for research involving children.

I confirm that the details of this study have been fully explained and described in writing to (insert name) and have been understood by him/her and I therefore consent to his/her participation in this study.

Signed : _____ Date : _____

Please provide a contact number in case we need to get in touch with you.

Telephone : _____

Appendix 4 – SF-36v2

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
○	○	○	○	○

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c. Lifting or carrying groceries	○	○	○
d. Climbing several flights of stairs	○	○	○
e. Climbing one flight of stairs	○	○	○
f. Bending, kneeling, or stooping	○	○	○
g. Walking more than a mile	○	○	○

h. Walking several hundred yards	○	○	○
i. Walking one hundred yards	○	○	○
j. Bathing or dressing yourself	○	○	○

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Were limited in the kind of work or other activities	○	○	○	○	○
d. Had difficulty performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○

c. Did work or activities less carefully than usual ○ ○ ○ ○ ○

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all ○ Slightly ○ Moderately ○ Quite a bit ○ Extremely ○

7. How much bodily pain have you had during the past 4 weeks?

None ○ Very Mild ○ Mild ○ Moderate ○ Severe ○ Very Severe ○

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely ○

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	○	○	○	○	○
b. Have you been very nervous?	○	○	○	○	○
c. Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d. Have you felt calm and peaceful?	○	○	○	○	○
e. Did you have a lot of energy?	○	○	○	○	○
f. Have you felt downhearted and depressed?	○	○	○	○	○

Nottingham Extended ADL Scale

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the last few weeks.

DID YOU…….	Not at all	with help	on your own	on your own with difficulty
1. Walk around outside?	☐	☐	☐	☐
2. Climb stairs?	☐	☐	☐	☐
3. Get in and out of a car?	☐	☐	☐	☐
4. Walk over uneven ground?	☐	☐	☐	☐
5. Cross roads?	☐	☐	☐	☐
6. Travel on public transport?	☐	☐	☐	☐
7. Manage to feed yourself?	☐	☐	☐	☐
8. Manage to make yourself a hot drink?	☐	☐	☐	☐
9. Take hot drinks from one room to another?	☐	☐	☐	☐
10. Do the washing up?	☐	☐	☐	☐
11. Make yourself a hot snack?	☐	☐	☐	☐

	No	With help	On your own with difficulty	On your own
12. Manage your own money when out?	☐	☐	☐	☐
13. Wash small items of clothing?	☐	☐	☐	☐
14. Do your own housework?	☐	☐	☐	☐
15. Do your own shopping?	☐	☐	☐	☐
16. Do a full clothes wash?	☐	☐	☐	☐
17. Read newspapers or books?	☐	☐	☐	☐
18. Use the telephone?	☐	☐	☐	☐
19. Write letters?	☐	☐	☐	☐
20. Go out socially?	☐	☐	☐	☐
21. Manage your own garden?	☐	☐	☐	☐
22. Drive a car?	☐	☐	☐	☐

Appendix 6 – Checklist Individual Strength

********* CIS20R_08 *********

Checklist Individual Strength

Radboud University Nijmegen Medical Centre, The Netherlands

Expert Centre Chronic Fatigue

Instruction:

On the next page you find 20 statements. With these statements we wish to get an impression of how you have felt during the last two weeks. For example:

I feel relaxed

If you feel that this statement is entirely true, tick the left box; as follows:

I feel relaxed	**yes**, that is true	X						**no**, that is not true

If you feel that this statement is not true at all, tick the right box; as follows:

I feel relaxed	**yes**, that is true						X	**no**, that is not true

If you feel that this statement is neither "yes, that is true", nor "no, that is not true", tick the box that is most in accordance with how you have felt.

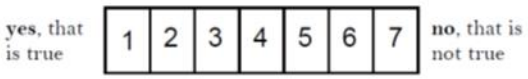
For example, if you feel relaxed, but not very relaxed, tick one of the boxes close to "yes, that is true": as follows:

I feel relaxed	**yes**, that is true			X				**no**, that is not true

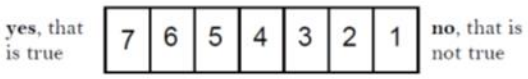
Do not skip any statement and tick each statement only once.

SCORING CIS20R_08

For the items: **2, 5, 6, 7, 8, 11, 12, 15, 20** is the scoring as follows:



For the items: **1, 3, 4, 9, 10, 13, 14, 16, 17, 18, 19** is the scoring as follows:



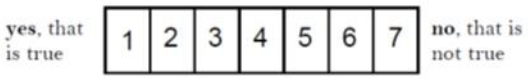
Subsequently **the four subscales** are calculated by summing the respective items. A higher the score means more problems.

subscale 1: Severity of fatigue	items 1, 4, 6, 9, 12, 14, 16, 20
subscale 2: Concentration problems	items 3, 8, 11, 13, 19
subscale 3: Decreased Motivation	items 2, 5, 15, 18
subscale 4: Decreased Physical Activity	items 7, 10, 17

1.	I feel tired.	yes, that is true							no, that is not true
2.	I feel very active.	yes, that is true							no, that is not true
3.	Thinking requires effort.	yes, that is true							no, that is not true
4.	Physically I feel exhausted.	yes, that is true							no, that is not true
5.	I feel like doing lots of nice things.	yes, that is true							no, that is not true
6.	I feel fit.	yes, that is true							no, that is not true
7.	I am physically very active.	yes, that is true							no, that is not true
8.	When I am doing something, I can keep my thoughts on it.	yes, that is true							no, that is not true
9.	I feel powerless.	yes, that is true							no, that is not true
10.	I am physically not very active.	yes, that is true							no, that is not true
11.	I find it easy to focus my mind.	yes, that is true							no, that is not true
12.	I am rested.	yes, that is true							no, that is not true
13.	It takes a lot of effort to concentrate on things.	yes, that is true							no, that is not true
14.	Physically I feel I am in bad form.	yes, that is true							no, that is not true
15.	I have a lot of plans.	yes, that is true							no, that is not true
16.	I tire easily.	yes, that is true							no, that is not true
17.	My level of physical activity is low.	yes, that is true							no, that is not true
18.	I don't feel like doing anything.	yes, that is true							no, that is not true
19.	My thoughts easily wander.	yes, that is true							no, that is not true
20.	Physically I feel I am in an excellent condition.	yes, that is true							no, that is not true

SCORING CIS20R_08

For the items: **2, 5, 6, 7, 8, 11, 12, 15, 20** is the scoring as follows:

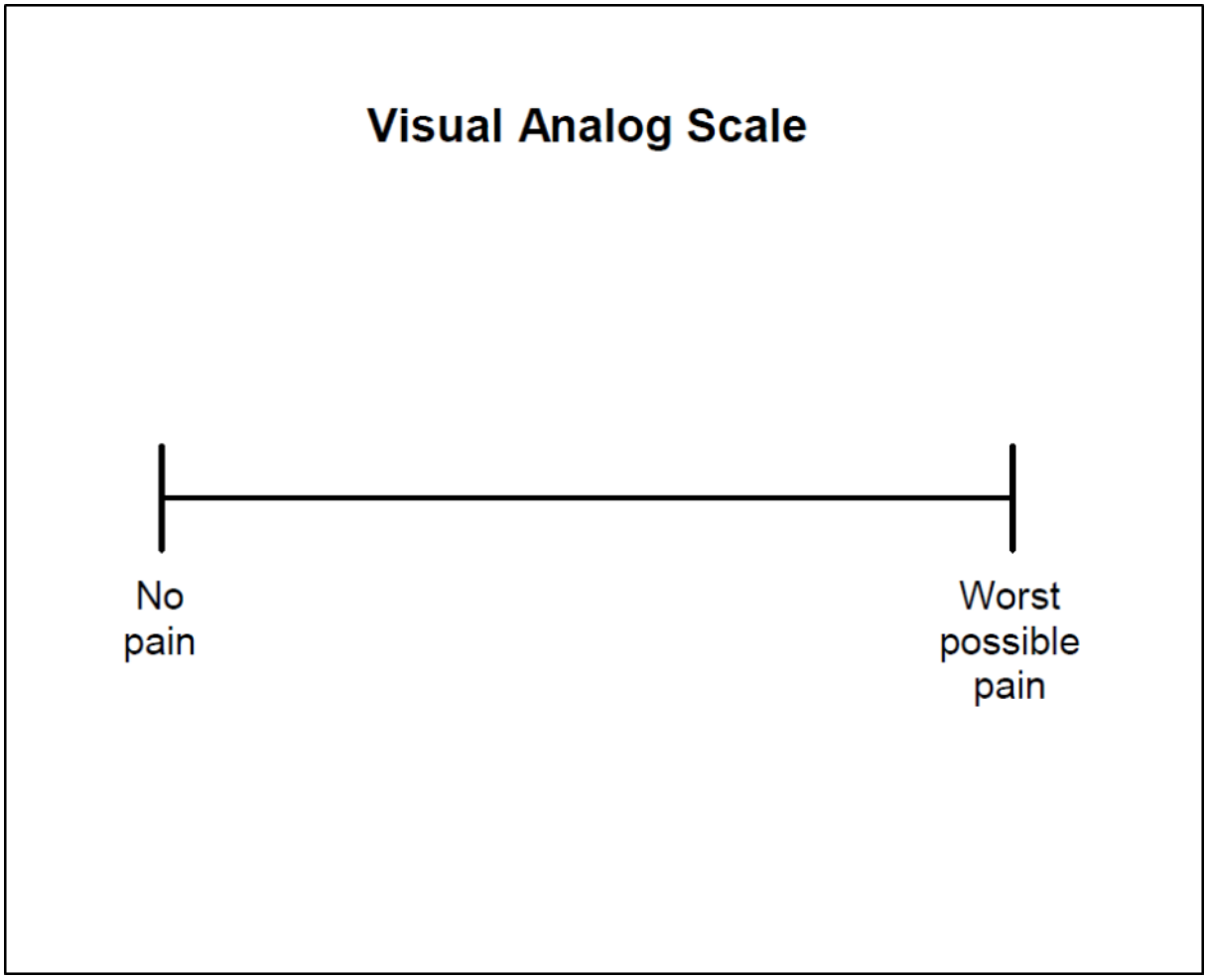


For the items: **1, 3, 4, 9, 10, 13, 14, 16, 17, 18, 19** is the scoring as follows:

Subsequently **the four subscales** are calculated by summing the respective items. A higher the score means more problems.

subscale 1: Severity of fatigue	items 1, 4, 6, 9, 12, 14, 16, 20
subscale 2: Concentration problems	items 3, 8, 11, 13, 19
subscale 3: Decreased Motivation	items 2, 5, 15, 18
subscale 4: Decreased Physical Activity	items 7, 10, 17

Appendix 7 – Pain Visual Analog Scale



Appendix 8 – General Self Efficacy Scale

General Self-Efficacy Scale

English version by Ralf Schwarzer & Matthias Jerusalem, 1995

	Not at all true	Hardly true	Moderately true	Exactly true
1. I can always manage to solve difficult problems if I try hard enough.	☐	☐	☐	☐
2. If someone opposes me, I can find the means and ways to get what I want.	☐	☐	☐	☐
3. It is easy for me to stick to my aims and accomplish my goals.	☐	☐	☐	☐
4. I am confident that I could deal efficiently with unexpected events.	☐	☐	☐	☐
5. Thanks to my resourcefulness, I know how to handle unforeseen situations.	☐	☐	☐	☐
6. I can solve most problems if I invest the necessary effort.	☐	☐	☐	☐
7. I can remain calm when facing difficulties because I can rely on my coping abilities.	☐	☐	☐	☐
8. When I am confronted with a problem, I can usually find several solutions.	☐	☐	☐	☐
9. If I am in trouble, I can usually think of a solution.	☐	☐	☐	☐
10. I can usually handle whatever comes my way.	☐	☐	☐	☐

Appendix 9 – SF-36 Walk-Wheel

The following questions are about activities you might do during a typical day. In the past 1-week does your health limit you in these activities? If so, how much?

(Please circle one number on each line)

	ACTIVITIES	Yes Limited A lot	Yes Limited A little	No, Not Limited At All
3a:	Vigorous activities, such as running, lifting heavy Objects, participating in strenuous sports	1	2	3
3b:	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3c:	Lifting or carrying groceries	1	2	3
3d:	Climbing several flights of stairs	1	2	3
3e:	Climbing one flight of stairs	1	2	3
3f:	Bending, kneeling, or stooping	1	2	3
3g:	Walking more than one kilometre	1	2	3
3h:	Walking half a kilometre	1	2	3
3i:	Walking 100 metres	1	2	3
3g ww:	Wheeling more than one kilometre	1	2	3
3h ww:	Wheeling half a kilometre	1	2	3
3i ww:	Wheeling 100 metres	1	2	3
3j:	Bathing or dressing yourself	1	2	3

[a]Modified from SF-36[1]: Items 3 (a to j) are the original SF-36 questions, while 3g ww to 3i ww (shaded area) comprise the supplementary SF-36ww modification.

Appendix 10 – Overview of Thesis Findings

Overview of Thesis findings presented with the main themes of impaired muscle strength and range of motion. SB% = Percentage of waking hours in sedentary behaviour, PA = Physical Activity, KEMVC = Knee extension maximal voluntary contraction, PFMVC = Plantar-flexion maximal voluntary contraction, QoL = Quality of Life, ROM = Range of Motion, $ROM^{Passive}$ = Passive range of motion, ROM^{Active} = Active range of motion, $DF^{Passive}$ = Passive dorsi-flexion, DMD = Duchenne muscular dystrophy, BMD = Becker's muscular dystrophy, LGMD = Limb-girdle muscular dystrophy, FSHD = Facioscapulohumeral muscular dystrophy. ROM

presentation is consistent with that presented in Figure 3.2: Superior black dotted line ( ) = $DF^{Passive}$; Inferior black dotted line ( ) = $PF^{Passive}$; Superior grey dotted line ( ) = DF^{Active}; Inferior grey dotted line ( ) – $PF^{Passive}$; Black solid line ( ) = Resting Angle. In Brief MTU Morphology: Filled black rectangle ( ) = Tibia; Unfilled black rectangle ( ) = Achilles tendon; Striated half-moon ( ) = Gastrocnemius medialis.

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